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(54) Title: NUCLEIC ACID MOLECULES AND PROTEINS FOR THE IDENTIFICATION, ASSESSMENT, PREVENTION, AND THERAPY OF OVARIAN CANCER

(57) Abstract: The invention relates to newly discovered nucleic acid molecules and proteins associated with ovarian cancer. Compositions, kits, and methods for detecting, characterizing, preventing, and treating human ovarian cancers are provided.

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NUCLEIC ACID MOLECULES AND PROTEINS FOR THE IDENTIFICATION,
ASSESSMENT, PREVENTION, AND THERAPY OF
OVARIAN CANCER

5 RELATED APPLICATIONS

The present application claims priority from U.S. provisional patent application serial no. 60/276,025, filed on March 14, 2001, which was abandoned on September 25, 2001, and from U.S. provisional patent application serial no. 60/325,149, filed on September 26, 2001. The present application also claims priority from U.S. provisional
10 patent application serial no. 60/276,026; filed on March 14, 2001, which was abandoned on September 25, 2001, and from U.S. provisional patent application serial no. 60/324,967, filed September 26, 2001. The present application additionally claims priority from U.S. provisional patent application serial no. 60/311,732, filed August 10, 2001, which was abandoned on September 25, 2001, and from U.S. provisional patent
15 application serial no. 60/325,102, filed September 26, 2001. The present application also claims priority from U.S. provisional patent application serial no. 60/323,580, filed September 19, 2001. All of the above applications are expressly incorporated by reference.

20 FIELD OF THE INVENTION

The field of the invention is ovarian cancer, including diagnosis, characterization, management, and therapy of ovarian cancer.

BACKGROUND OF THE INVENTION

25 Ovarian cancer is responsible for significant morbidity and mortality in populations around the world. Ovarian cancer is classified, on the basis of clinical and pathological features, in three groups, namely epithelial ovarian cancer (EOC; >90% of ovarian cancer in Western countries), germ cell tumors (*circa* 2-3% of ovarian cancer), and stromal ovarian cancer (*circa* 5% of ovarian cancer; Ozols *et al.*, 1997, *Cancer*
30 *Principles and Practice of Oncology*, 5th ed., DeVita *et al.*, Eds. pp. 1502). Relative to EOC, germ cell tumors and stromal ovarian cancers are more easily detected and treated

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at an early stage, translating into higher/better survival rates for patients afflicted with these two types of ovarian cancer.

There are numerous types of ovarian tumors, some of which are benign, and others of which are malignant. Treatment (including non-treatment) options and predictions of patient outcome depend on accurate classification of the ovarian cancer. Ovarian cancers are named according to the type of cells from which the cancer is derived and whether the ovarian cancer is benign or malignant. Recognized histological tumor types include, for example, serous, mucinous, endometrioid, and clear cell tumors. In addition, ovarian cancers are classified according to recognized grade and stage scales.

In grade I, the tumor tissue is well differentiated. In grade II, tumor tissue is moderately well differentiated. In grade III, the tumor tissue is poorly differentiated. This grade correlates with a less favorable prognosis than grades I and II. Stage I is generally confined within the capsule surrounding one (stage IA) or both (stage IB) ovaries, although in some stage I (*i.e.* stage IC) cancers, malignant cells may be detected in ascites, in peritoneal rinse fluid, or on the surface of the ovaries. Stage II involves extension or metastasis of the tumor from one or both ovaries to other pelvic structures. In stage IIA, the tumor extends or has metastasized to the uterus, the fallopian tubes, or both. Stage IIB involves extension of the tumor to the pelvis. Stage IIC is stage IIA or IIB in which malignant cells may be detected in ascites, in peritoneal rinse fluid, or on the surface of the ovaries. In stage III, the tumor comprises at least one malignant extension to the small bowel or the omentum, has formed extrapelvic peritoneal implants of microscopic (stage IIIA) or macroscopic (< 2 centimeter diameter, stage IIIB; > 2 centimeter diameter, stage IIIC) size, or has metastasized to a retroperitoneal or inguinal lymph node (an alternate indicator of stage IIIC). In stage IV, distant (*i.e.* non-peritoneal) metastases of the tumor can be detected.

The durations of the various stages of ovarian cancer are not presently known, but are believed to be at least about a year each (Richart *et al.*, 1969, *Am. J. Obstet. Gynecol.* 105:386). Prognosis declines with increasing stage designation. For example, 5-year survival rates for patients diagnosed with stage I, II, III, and IV ovarian cancer are 80%, 57%, 25%, and 8%, respectively.

Despite being the third most prevalent gynecological cancer, ovarian cancer is the leading cause of death among those afflicted with gynecological cancers. The disproportionate mortality of ovarian cancer is attributable to a substantial absence of symptoms among those afflicted with early-stage ovarian cancer and to difficulty
5 diagnosing ovarian cancer at an early stage. Patients afflicted with ovarian cancer most often present with non-specific complaints, such as abnormal vaginal bleeding, gastrointestinal symptoms, urinary tract symptoms, lower abdominal pain, and generalized abdominal distension. These patients rarely present with paraneoplastic symptoms or with symptoms which clearly indicate their affliction. Presently, less than
10 about 40% of patients afflicted with ovarian cancer present with stage I or stage II. Management of ovarian cancer would be significantly enhanced if the disease could be detected at an earlier stage, when treatments are much more generally efficacious.

Ovarian cancer may be diagnosed, in part, by collecting a routine medical history from a patient and by performing physical examination, x-ray examination, and
15 chemical and hematological studies on the patient. Hematological tests which may be indicative of ovarian cancer in a patient include analyses of serum levels of proteins designated CA125 and DF3 and plasma levels of lysophosphatidic acid (LPA). Palpation of the ovaries and ultrasound techniques (particularly including endovaginal ultrasound and color Doppler flow ultrasound techniques) can aid detection of ovarian
20 tumors and differentiation of ovarian cancer from benign ovarian cysts. However, a definitive diagnosis of ovarian cancer typically requires performing exploratory laparotomy of the patient.

Potential tests for the detection of ovarian cancer (*e.g.*, screening, reflex or monitoring) may be characterized by a number of factors. The "sensitivity" of an
25 assay refers to the probability that the test will yield a positive result in an individual afflicted with ovarian cancer. The "specificity" of an assay refers to the probability that the test will yield a negative result in an individual not afflicted with ovarian cancer. The "positive predictive value" (PPV) of an assay is the ratio of true positive results (*i.e.* positive assay results for patients afflicted with ovarian cancer) to all positive results
30 (*i.e.* positive assay results for patients afflicted with ovarian cancer + positive assay results for patients not afflicted with ovarian cancer). It has been estimated that in order for an assay to be an appropriate population-wide screening tool for ovarian cancer the

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assay must have a PPV of at least about 10% (Rosenthal *et al.*, 1998, *Sem. Oncol.* 25:315-325). It would thus be desirable for a screening assay for detecting ovarian cancer in patients to have a high sensitivity and a high PPV. Monitoring and reflex tests would also require appropriate specifications.

5 Owing to the cost, limited sensitivity, and limited specificity of known methods of detecting ovarian cancer, screening is not presently performed for the general population. In addition, the need to perform laparotomy in order to diagnose ovarian cancer in patients who screen positive for indications of ovarian cancer limits the desirability of population-wide screening, such that a PPV even greater than 10%
10 would be desirable.

 Prior use of serum CA125 level as a diagnostic marker for ovarian cancer indicated that this method exhibited insufficient specificity for use as a general screening method. Use of a refined algorithm for interpreting CA125 levels in serial retrospective samples obtained from patients improved the specificity of the method
15 without shifting detection of ovarian cancer to an earlier stage (Skakes, 1995, *Cancer* 76:2004). Screening for LPA to detect gynecological cancers including ovarian cancer exhibited a sensitivity of about 96% and a specificity of about 89%. However, CA125-based screening methods and LPA-based screening methods are hampered by the presence of CA125 and LPA, respectively, in the serum of patients afflicted with
20 conditions other than ovarian cancer. For example, serum CA125 levels are known to be associated with menstruation, pregnancy, gastrointestinal and hepatic conditions such as colitis and cirrhosis, pericarditis, renal disease, and various non-ovarian malignancies. Serum LPA is known, for example, to be affected by the presence of non-ovarian gynecological malignancies. A screening method having a greater specificity for
25 ovarian cancer than the current screening methods for CA125 and LPA could provide a population-wide screening for early stage ovarian cancer.

 Presently greater than about 60% of ovarian cancers diagnosed in patients are stage III or stage IV cancers. Treatment at these stages is largely limited to cytoreductive surgery (when feasible) and chemotherapy, both of which aim to slow the
30 spread and development of metastasized tumor. Substantially all late stage ovarian cancer patients currently undergo combination chemotherapy as primary treatment, usually a combination of a platinum compound and a taxane. Median survival for

responding patients is about one year. Combination chemotherapy involving agents such as doxorubicin, cyclophosphamide, cisplatin, hexamethylmelamine, paclitaxel, and methotrexate may improve survival rates in these groups, relative to single-agent therapies. Various recently-developed chemotherapeutic agents and treatment regimens have also demonstrated usefulness for treatment of advanced ovarian cancer. For example, use of the topoisomerase I inhibitor topectan, use of amifostine to minimize chemotherapeutic side effects, and use of intraperitoneal chemotherapy for patients having peritoneally implanted tumors have demonstrated at least limited utility. Presently, however, the 5-year survival rate for patients afflicted with stage III ovarian cancer is 25%, and the survival rate for patients afflicted with stage IV ovarian cancer is 8%.

In summary, the earlier ovarian cancer is detected, the aggressiveness of therapeutic intervention and the side effects associated with therapeutic intervention are minimized. More importantly, the earlier the cancer is detected, the survival rate and quality of life of ovarian cancer patients is enhanced. Thus, a pressing need exists for methods of detecting ovarian cancer as early as possible. There also exists a need for methods of detecting recurrence of ovarian cancer as well as methods for predicting and monitoring the efficacy of treatment. There further exists a need for new therapeutic methods for treating ovarian cancer. The present invention satisfies these needs.

SUMMARY OF THE INVENTION

The invention relates to cancer markers (hereinafter "markers" or "markers of the inventions"), which are listed in Tables 1-3. The invention provides nucleic acids and proteins that are encoded by or correspond to the markers (hereinafter "marker nucleic acids" and "marker proteins," respectively). The invention further provides antibodies, antibody derivatives and antibody fragments which bind specifically with such proteins and/or fragments of the proteins.

In one aspect, the invention relates to various diagnostic, monitoring, test and other methods related to ovarian cancer detection and therapy. In one embodiment, the invention provides a diagnostic method of assessing whether a patient has ovarian cancer or has higher than normal risk for developing ovarian cancer, comprising the steps of comparing the level of expression of a marker of the invention in a patient

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sample and the normal level of expression of the marker in a control, *e.g.*, a sample from a patient without ovarian cancer. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with ovarian cancer or has higher than normal risk for developing
5 ovarian cancer.

In a preferred embodiment of the diagnostic method, the marker is over-expressed by at least two-fold in at least about 20% of stage I ovarian cancer patients, stage II ovarian cancer patients, stage III ovarian cancer patients, stage IV ovarian cancer patients, grade I ovarian cancer patients, grade II ovarian cancer patients, grade
10 III ovarian cancer patients, epithelial ovarian cancer patients, stromal ovarian cancer patients, germ cell ovarian cancer patients, malignant ovarian cancer patients, benign ovarian cancer patients, serous neoplasm ovarian cancer patients, mucinous neoplasm ovarian cancer patients, endometrioid neoplasm ovarian cancer patients and/or clear cell neoplasm ovarian cancer patients.

15 The diagnostic methods of the present invention are particularly useful for patients with an identified pelvic mass or symptoms associated with ovarian cancer. The methods of the present invention can also be of particular use with patients having an enhanced risk of developing ovarian cancer (*e.g.*, patients having a familial history of ovarian cancer, patients identified as having a mutant oncogene, and patients at least
20 about 50 years of age).

In a preferred diagnostic method of assessing whether a patient is afflicted with ovarian cancer (*e.g.*, new detection ("screening"), detection of recurrence, reflex testing), the method comprises comparing:

- a) the level of expression of a marker of the invention in a patient sample,
25 and
- b) the normal level of expression of the marker in a control non-ovarian cancer sample.

A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with ovarian
30 cancer.

The invention also provides diagnostic methods for assessing the efficacy of a therapy for inhibiting ovarian cancer in a patient. Such methods comprise comparing:

- 5 a) expression of a marker of the invention in a first sample obtained from the patient prior to providing at least a portion of the therapy to the patient, and
- b) expression of the marker in a second sample obtained from the patient following provision of the portion of the therapy.

10 A significantly lower level of expression of the marker in the second sample relative to that in the first sample is an indication that the therapy is efficacious for inhibiting ovarian cancer in the patient.

It will be appreciated that in these methods the "therapy" may be any therapy for treating ovarian cancer including, but not limited to, chemotherapy, radiation therapy, surgical removal of tumor tissue, gene therapy and biologic therapy such as the
15 administering of antibodies and chemokines. Thus, the methods of the invention may be used to evaluate a patient before, during and after therapy, for example, to evaluate the reduction in tumor burden.

In a preferred embodiment, the diagnostic methods of the present invention are directed to therapy using a chemical or biologic agent. These methods
20 comprise comparing:

- a) expression of a marker of the invention in a first sample obtained from the patient and maintained in the presence of the chemical or biologic agent, and
- 25 b) expression of the marker in a second sample obtained from the patient and maintained in the absence of the agent.

A significantly lower level of expression of the marker in the first sample relative to that in the second sample is an indication that the agent is efficacious for inhibiting ovarian cancer in the patient. In one embodiment, the first and second samples can be portions of a single sample obtained from the patient or portions of pooled samples obtained
30 from the patient.

The invention additionally provides a monitoring method for assessing the progression of ovarian cancer in a patient, the method comprising:

- a) detecting in a patient sample at a first time point, the expression of a marker of the invention;
- 5 b) repeating step a) at a subsequent time point in time; and
- c) comparing the level of expression detected in steps a) and b), and therefrom monitoring the progression of ovarian cancer in the patient.

A significantly higher level of expression of the marker in the sample at the subsequent time point from that of the sample at the first time point is an indication that the ovarian
10 cancer has progressed, whereas a significantly lower level of expression is an indication that the ovarian cancer has regressed.

The invention further provides a diagnostic method for determining whether ovarian cancer has metastasized or is likely to metastasize in the future, the method comprising comparing:

- 15 a) the level of expression of a marker of the invention in a patient sample, and
- b) the normal level (or non-metastatic level) of expression of the marker in a control sample.

A significantly higher level of expression in the patient sample as compared to the
20 normal level (or non-metastatic level) is an indication that the ovarian cancer has metastasized or is likely to metastasize in the future.

The invention moreover provides a test method for selecting a composition for inhibiting ovarian cancer in a patient. This method comprises the steps of:

- 25 a) obtaining a sample comprising cancer cells from the patient;
- b) separately maintaining aliquots of the sample in the presence of a plurality of test compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- 30 d) selecting one of the test compositions which significantly reduces the level of expression of the marker in the aliquot containing that test

composition, relative to the levels of expression of the marker in the presence of the other test compositions.

The invention additionally provides a test method of assessing the ovarian carcinogenic potential of a compound. This method comprises the steps of:

- 5 a) maintaining separate aliquots of ovarian cells in the presence and absence of the compound; and
- b) comparing expression of a marker of the invention in each of the aliquots.

A significantly higher level of expression of the marker in the aliquot maintained in the presence of the compound, relative to that of the aliquot maintained in the absence of the compound, is an indication that the compound possesses ovarian carcinogenic potential.

In addition, the invention further provides a method of inhibiting ovarian cancer in a patient. This method comprises the steps of:

- a) obtaining a sample comprising cancer cells from the patient;
- 15 b) separately maintaining aliquots of the sample in the presence of a plurality of compositions;
- c) comparing expression of a marker of the invention in each of the aliquots; and
- d) administering to the patient at least one of the compositions which
- 20 significantly lowers the level of expression of the marker in the aliquot containing that composition, relative to the levels of expression of the marker in the presence of the other compositions.

In the aforementioned methods, the samples or patient samples comprise cells obtained from the patient. The cells may be found in an ovarian tissue sample

25 collected, for example, by an ovarian tissue biopsy or histology section. In one embodiment, the patient sample is an ovary-associated body fluid. Such fluids include, for example, blood fluids, lymph, ascites fluids, gynecological fluids, cystic fluids, urine, and fluids collected by peritoneal rinsing. In another embodiment, the sample comprises cells obtained from the patient. In this embodiment, the cells may be found in

30 a fluid selected from the group consisting of a fluid collected by peritoneal rinsing, a fluid collected by uterine rinsing, a uterine fluid, a uterine exudate, a pleural fluid, and an ovarian exudate. In a further embodiment, the patient sample is *in vivo*.

According to the invention, the level of expression of a marker of the invention in a sample can be assessed, for example, by detecting the presence in the sample of:

- the corresponding marker protein or a fragment of the protein (*e.g.* by using a reagent, such as an antibody, an antibody derivative, an antibody fragment or single-chain antibody, which binds specifically with the protein or protein fragment).
- the corresponding marker nucleic acid or a fragment of the nucleic acid (*e.g.* by contacting transcribed polynucleotides obtained from the sample with a substrate having affixed thereto one or more nucleic acids having the entire or a segment of the sequence or a complement thereof)
- a metabolite which is produced directly (*i.e.*, catalyzed) or indirectly by the corresponding marker protein.

According to the invention, any of the aforementioned methods may be performed using a plurality (*e.g.* 2, 3, 5, or 10 or more) of ovarian cancer markers, including ovarian cancer markers known in the art. In such methods, the level of expression in the sample of each of a plurality of markers, at least one of which is a marker of the invention, is compared with the normal level of expression of each of the plurality of markers in samples of the same type obtained from control humans not afflicted with ovarian cancer. A significantly altered (*i.e.*, increased or decreased as specified in the above-described methods using a single marker) level of expression in the sample of one or more markers of the invention, or some combination thereof, relative to that marker's corresponding normal levels, is an indication that the patient is afflicted with ovarian cancer. For all of the aforementioned methods, the marker(s) are preferably selected such that the positive predictive value of the method is at least about 10%.

In a further aspect, the invention provides an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein or a fragment of the protein. The invention also provides methods for making such antibody, antibody derivative, and antibody fragment. Such methods may comprise immunizing a mammal with a protein or peptide comprising the entirety, or a segment of 10 amino acids or more, of a marker protein, wherein the protein or peptide may be obtained from

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a cell or by chemical synthesis. The methods of the invention also encompass producing monoclonal and single-chain antibodies, which would further comprise isolating splenocytes from the immunized mammal, fusing the isolated splenocytes with an immortalized cell line to form hybridomas, and screening individual hybridomas for those that produce an antibody that binds specifically with a marker protein or a fragment of the protein.

In another aspect, the invention relates to various diagnostic and test kits. In one embodiment, the invention provides a kit for assessing whether a patient is afflicted with ovarian cancer. The kit comprises a reagent for assessing expression of a marker of the invention. In another embodiment, the invention provides a kit for assessing the suitability of a chemical or biologic agent for inhibiting an ovarian cancer in a patient. Such kit comprises a reagent for assessing expression of a marker of the invention, and may also comprise one or more of such agents. In a further embodiment, the invention provides kits for assessing the presence of ovarian cancer cells or treating ovarian cancers. Such kits comprise an antibody, an antibody derivative, or an antibody fragment, which binds specifically with a marker protein, or a fragment of the protein. Such kits may also comprise a plurality of antibodies, antibody derivatives, or antibody fragments wherein the plurality of such antibody agents binds specifically with a marker protein, or a fragment of the protein.

In an additional embodiment, the invention also provides a kit for assessing the presence of ovarian cancer cells, wherein the kit comprises a nucleic acid probe that binds specifically with a marker nucleic acid or a fragment of the nucleic acid. The kit may also comprise a plurality of probes, wherein each of the probes binds specifically with a marker nucleic acid, or a fragment of the nucleic acid.

In a further aspect, the invention relates to methods for treating a patient afflicted with ovarian cancer or at risk of developing ovarian cancer. Such methods may comprise reducing the expression and/or interfering with the biological function of a marker of the invention. In one embodiment, the method comprises providing to the patient an antisense oligonucleotide or polynucleotide complementary to a marker nucleic acid, or a segment thereof. For example, an antisense polynucleotide may be provided to the patient through the delivery of a vector that expresses an antisense polynucleotide of a marker nucleic acid or a fragment thereof. In another embodiment,

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the method comprises providing to the patient an antibody, an antibody derivative, or antibody fragment, which binds specifically with a marker protein or a fragment of the protein. In a preferred embodiment, the antibody, antibody derivative or antibody fragment binds specifically with a protein having the sequence of any of the markers
5 listed in Table 1, or a fragment of such a protein.

It will be appreciated that the methods and kits of the present invention may also include known cancer markers including known ovarian cancer markers. It will further be appreciated that the methods and kits may be used to identify cancers other than ovarian cancer.

10

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 depicts a graph which represents the results of the TaqMan® expression study.

15

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to newly discovered markers, identified in Tables 1-3, that are associated with the cancerous state of ovarian cells. It has been discovered that the higher than normal level of expression of any of these markers or combination of these markers correlates with the presence of ovarian cancer in a patient. Methods
20 are provided for detecting the presence of ovarian cancer in a sample, the absence of ovarian cancer in a sample, the stage of an ovarian cancer, and with other characteristics of ovarian cancer that are relevant to prevention, diagnosis, characterization, and therapy of ovarian cancer in a patient. Methods of treating ovarian cancer are also provided.

Tables 1-3 list the markers of the present invention. In the Tables the
25 markers are identified with a name ("Marker"), the name the gene is commonly known by, if applicable ("Gene Name"), the Sequence Listing identifier of the cDNA sequence of a nucleotide transcript encoded by or corresponding to the marker ("SEQ ID NO (nts)"), the Sequence Listing identifier of the amino acid sequence of a protein encoded by the nucleotide transcript ("SEQ ID NO (AAs)"), and the location of the protein
30 coding sequence within the cDNA sequence ("CDS").

Table 1 lists all of the markers of the invention, which are over-expressed in ovarian cancer cells compared to normal (*i.e.*, non-cancerous) ovarian cells and comprises markers listed in Tables 2 and 3. Table 2 lists newly-identified nucleotide

and amino acid sequences useful as ovarian cancer markers. Table 3 lists newly-identified nucleotide sequences useful as ovarian cancer markers.

In addition to their use in ovarian cancer, it has been found that the markers of the present invention may be used in the diagnosis, characterization, management, and therapy of additional diseases. For example, OV65 (SEQ ID NOS: 305 and 306), M593 (SEQ ID NOS: 307 and 308) and M594 (SEQ ID NOS: 309 and 310), are spondin molecules, and have one or more of the following activities: (1) neural cell adhesion and (2) neurite extension and can thus be used in, for example, the diagnosis and treatment of brain and CNS related disorders. Such brain and CNS related disorders include, but are not limited to, bacterial and viral meningitis, Alzheimers Disease, cerebral toxoplasmosis, Parkinson's disease, multiple sclerosis, brain cancers (*e.g.*, metastatic carcinoma of the brain, glioblastoma, lymphoma, astrocytoma, acoustic neuroma), hydrocephalus, and encephalitis. In another example, OV65, M593 and M594 polypeptides, nucleic acids, and modulators thereof can be used to treat disorders of the brain, such as cerebral edema, hydrocephalus, brain herniations, iatrogenic disease (due to, *e.g.*, infection, toxins, or drugs), inflammations (*e.g.*, bacterial and viral meningitis, encephalitis, and cerebral toxoplasmosis), cerebrovascular diseases (*e.g.*, hypoxia, ischemia, infarction, intracranial hemorrhage, vascular malformations, and hypertensive encephalopathy), and tumors (*e.g.*, neuroglial tumors, neuronal tumors, tumors of pineal cells, meningeal tumors, primary and secondary lymphomas, intracranial tumors, and medulloblastoma), and to treat injury or trauma to the brain.

OV25 (SEQ ID NOS: 360 and 361), an HE4 protein, has one or more of the following activities: (1) sperm maturation and (2) inhibition of extracellular proteases and can thus be used in, for example, the treatment and diagnosis of diseases and disorders relating to spermatogenesis. For example, OV25 polypeptides, nucleic acids, and modulators thereof can be used to treat testicular disorders, such as unilateral testicular enlargement (*e.g.*, nontuberculous, granulomatous orchitis); inflammatory diseases resulting in testicular dysfunction (*e.g.*, gonorrhea and mumps); cryptorchidism; sperm cell disorders (*e.g.*, immotile cilia syndrome and germinal cell aplasia); acquired testicular defects (*e.g.*, viral orchitis); and tumors (*e.g.*, germ cell tumors, interstitial cell tumors, androblastoma, testicular lymphoma and adenomatoid tumors).

OV52 (SEQ ID NOS: 190 and 191), a Pump-1 proteinase, has been found to have one or more of the following activities: (1) breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and remodeling, as well as in (2) disease processes, such as arthritis, and metastasis. Hence, 5 OV52 nucleic acids, proteins, and modulators thereof can be used to modulate disorders associated with adhesion and migration of cells, *e.g.*, platelet aggregation disorders (*e.g.*, Glanzmann's thromboasthenia, which is a bleeding disorder characterized by failure of platelet aggregation in response to cell stimuli), inflammatory disorders (*e.g.*, leukocyte adhesion deficiency, which is a disorder associated with impaired migration of 10 neutrophils to sites of extravascular inflammation), connective tissue disorders, arthritis, disorders associated with abnormal tissue migration during embryo development, and tumor metastasis.

M604 (SEQ ID NOS: 48 and 49), OV10 (SEQ ID NOS: 50 and 51), and M360 (SEQ ID NOS: 52 and 53), are Claudin molecules which have one or more of the 15 following activities: (1) it elicits fluid accumulation in the intestinal tract by altering the membrane permeability of intestinal epithelial cells and (2) thus acts as the causative agent of diarrhea. The polypeptides, nucleic acids, and modulators thereof can be used to treat colonic disorders, such as congenital anomalies (*e.g.*, megacolon and imperforate anus), idiopathic disorders (*e.g.*, diverticular disease and melanosis coli), vascular 20 lesions (*e.g.*, ischemic colitis, hemorrhoids, angiodysplasia), inflammatory diseases (*e.g.*, colitis (*e.g.*, idiopathic ulcerative colitis, pseudomembranous colitis), and lymphopathia venereum), Crohn's disease, and tumors (*e.g.*, hyperplastic polyps, adenomatous polyps, bronchogenic cancer, colonic carcinoma, squamous cell carcinoma, adenoacanthomas, sarcomas, lymphomas, argentaffinomas, carcinoids, and 25 melanocarcinomas).

OV48 (SEQ ID NOS: 226 and 227), OV49 (SEQ ID NOS: 228 and 229) and OV50 (SEQ ID NOS: 230 and 231), markers for an osteopontin protein, have one or more of the following activities: (1) they act as a vessel extracellular matrix protein involved in calcification and (2) atherosclerosis. Hence, OV48, OV49 and OV50 30 nucleic acids, proteins, and modulators thereof can be used to treat heart disorders, *e.g.*, ischemic heart disease, atherosclerosis, hypertension, angina pectoris, Hypertrophic Cardiomyopathy, and congenital heart disease. They can also be used to treat

cardiovascular disorders, such as ischemic heart disease (*e.g.*, angina pectoris, myocardial infarction, and chronic ischemic heart disease), hypertensive heart disease, pulmonary heart disease, valvular heart disease (*e.g.*, rheumatic fever and rheumatic heart disease, endocarditis, mitral valve prolapse, and aortic valve stenosis), congenital heart disease (*e.g.*, valvular and vascular obstructive lesions, atrial or ventricular septal defect, and patent ductus arteriosus), or myocardial disease (*e.g.*, myocarditis, congestive cardiomyopathy, and hypertrophic cardiomyopathy).

OV37 (SEQ ID NOS: 176 and 177), a lipocalin marker, is known to be a component of the neutrophil gelatinase complex. OV37 nucleic acids, proteins, and modulators thereof can be used to modulate the proliferation, differentiation, and/or function of leukocytes. Thus, OV37 nucleic acids, proteins, and modulators thereof can be used to treat bone marrow, blood, and hematopoietic associated diseases and disorders, *e.g.*, acute myeloid leukemia, hemophilia, leukemia, anemia (*e.g.*, sickle cell anemia), and thalassemia. OV37 polypeptides, nucleic acids, and modulators thereof can be used to treat leukocytic disorders, such as leukopenias (*e.g.*, neutropenia, monocytopenia, lymphopenia, and granulocytopenia), leukocytosis (*e.g.*, granulocytosis, lymphocytosis, eosinophilia, monocytosis, acute and chronic lymphadenitis), malignant lymphomas (*e.g.*, Non-Hodgkin's lymphomas, Hodgkin's lymphomas, leukemias, agnogenic myeloid metaplasia, multiple myeloma, plasmacytoma, Waldenstrom's macroglobulinemia, heavy-chain disease, monoclonal gammopathy, histiocytoses, eosinophilic granuloma, and angioimmunoblastic lymphadenopathy).

OV2 (SEQ ID NOS: 285 and 286), is known to be a protease inhibitor, which is associated with emphysema and liver disease. Hence OV2 polypeptides, nucleic acids, and modulators thereof can be used to diagnose and treat pulmonary (lung) disorders, such as atelectasis, cystic fibrosis, rheumatoid lung disease, pulmonary congestion or edema, chronic obstructive airway disease (*e.g.*, emphysema, chronic bronchitis, bronchial asthma, and bronchiectasis), diffuse interstitial diseases (*e.g.*, sarcoidosis, pneumoconiosis, hypersensitivity pneumonitis, bronchiolitis, Goodpasture's syndrome, idiopathic pulmonary fibrosis, idiopathic pulmonary hemosiderosis, pulmonary alveolar proteinosis, desquamative interstitial pneumonitis, chronic interstitial pneumonia, fibrosing alveolitis, hamman-rich syndrome, pulmonary eosinophilia, diffuse interstitial fibrosis, Wegener's granulomatosis, lymphomatoid

granulomatosis, and lipid pneumonia), or tumors (*e.g.*, bronchogenic carcinoma, bronchioloalveolar carcinoma, bronchial carcinoid, hamartoma, and mesenchymal tumors). In another example, OV2 polypeptides, nucleic acids, and modulators thereof can be used to diagnose and treat hepatic (liver) disorders, such as jaundice, hepatic failure, hereditary hyperbilirubinemias (*e.g.*, Gilbert's syndrome, Crigler-Najjar syndromes and Dubin-Johnson and Rotor's syndromes), hepatic circulatory disorders (*e.g.*, hepatic vein thrombosis and portal vein obstruction and thrombosis), hepatitis (*e.g.*, chronic active hepatitis, acute viral hepatitis, and toxic and drug-induced hepatitis), cirrhosis (*e.g.*, alcoholic cirrhosis, biliary cirrhosis, and hemochromatosis), or malignant tumors (*e.g.*, primary carcinoma, hepatoma, hepatoblastoma, liver cysts, and angiosarcoma).

OV32 (SEQ ID NOS: 166 and 167) and OV33 (SEQ ID NOS: 168 and 169), kallikrein markers, are useful in detection of primary mammary carcinomas, as well as primary ovarian cancers. Hence, OV32 and OV33 polypeptides, nucleic acids, and modulators thereof can be used to diagnose and treat ovarian disorders, such as ovarian endometriosis, non-neoplastic cysts (*e.g.*, follicular and luteal cysts and polycystic ovaries) and tumors (*e.g.*, carcinomas, tumors of surface epithelium, germ cell tumors, ovarian fibroma, sex cord-stromal tumors, and ovarian cancers (*e.g.*, metastatic carcinomas, and ovarian teratoma)).

OV68 (SEQ ID NOS: 192 and 193), OV69 (SEQ ID NOS: 194 and 195), OV70 (SEQ ID NOS: 196 and 197), OV71 (SEQ ID NOS: 198 and 199), OV72 (SEQ ID NOS: 200 and 201), OV41 (SEQ ID NOS: 202 and 203), OV42 (SEQ ID NOS: 204 and 205), OV43 (SEQ ID NOS: 206 and 205), OV44 (SEQ ID NOS: 207 and 208) and OV83 (SEQ ID NOS: 209 and 210), are all mesothelin markers, and have been found to play a role in cellular adhesion. The nucleic acids, proteins, and modulators thereof can be used to diagnose, treat and modulate disorders associated with adhesion and migration of cells, *e.g.*, platelet aggregation disorders (*e.g.*, Glanzmann's thrombasthenia, which is a bleeding disorder characterized by failure of platelet aggregation in response to cell stimuli), inflammatory disorders (*e.g.*, leukocyte adhesion deficiency, which is a disorder associated with impaired migration of neutrophils to sites of extravascular inflammation), disorders associated with abnormal tissue migration during embryo development, and tumor metastasis.

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OV17 (SEQ ID NOS: 110 and 111), OV18 (SEQ ID NOS: 112 and 111),
OV19 (SEQ ID NOS: 113 and 111), OV20 (SEQ ID NOS: 114 and 111), OV21 (SEQ
ID NOS: 115 and 111) and OV22 (SEQ ID NOS: 116 and 117) are folate receptors,
which are known to be markers of ovarian cancer. The nucleic acids, proteins, and
5 modulators thereof can be used to diagnose, treat and modulate ovarian disorders (*e.g.*,
ovarian cyst, ovarian fibroma, ovarian endometriosis, ovarian teratoma). Although these
markers have been previously associated with ovarian cancer, the expression of such
markers has not yet been identified in combination with the expression of other markers
including those of the present invention. Such combination of markers will provide
10 improved methods of diagnosing, characterizing, managing and treating ovarian cancer.

OV66 (SEQ ID NOS: 54 and 55), OV7 (SEQ ID NOS: 56 and 57), OV8
(SEQ ID NOS: 58 and 59) and OV81 (SEQ ID NOS: 60 and 61) are ceruloplasmin
markers, known to encode a plasma metalloprotein that binds copper in the plasma. The
nucleic acids, proteins, and modulators thereof can be used to diagnose, treat and
15 modulate disorders in blood haemostasis and diseases caused by such an imbalance *e.g.*,
(1) cardiovascular diseases or disorders, such as ischemic heart disease (*e.g.*, angina
pectoris, myocardial infarction, and chronic ischemic heart disease), hypertensive heart
disease, pulmonary heart disease, valvular heart disease (*e.g.*, rheumatic fever and
rheumatic heart disease, endocarditis, mitral valve prolapse, and aortic valve stenosis),
20 congenital heart disease (*e.g.*, valvular and vascular obstructive lesions, atrial or
ventricular septal defect, and patent ductus arteriosus), or myocardial disease (*e.g.*,
myocarditis, congestive cardiomyopathy, and hypertrophic cardiomyopathy); (2) neuronal
diseases such as Alzheimers Disease, cerebral toxoplasmosis, Parkinson's disease,
multiple sclerosis, brain cancers (*e.g.*, metastatic carcinoma of the brain, glioblastoma,
25 lymphoma, astrocytoma, acoustic neuroma), hydrocephalus, and encephalitis; and (3)
Wilson's Disease.

TABLE 1

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
OV1	ABCB1: ATP-binding cassette, sub-family B (MDR/TAP), member 1	1	2	425..4264
M430	ADPRT: ADP-ribosyltransferase	3	4	160..3204
M571	ANXA2: annexin A2, variant 1	5	6	134..1153
M572	ANXA2: annexin A2, variant 2	7	8	50..1069
M573	ANXA4: annexin A4	9	10	74..1039
OV3	AQP5: aquaporin 5	11	12	519..1316
M352	ARHGAP8: Rho GTPase activating protein 8, variant 1	13	14	142..1536
M353	ARHGAP8: Rho GTPase activating protein 8, variant 2	15	16	1..2043
M354	ARHGAP8: Rho GTPase activating protein 8, variant 3	17	18	1..2256
M608	ARHGAP8: Rho GTPase activating protein 8, variant 4	17	19	1..2157
M355	ARHGAP8: Rho GTPase activating protein 8, variant 5	20	21	<1..1314
M356	ARHGAP8: Rho GTPase activating protein 8, variant 6	22	23	1..1902
M357	ARHGAP8: Rho GTPase activating protein 8, variant 7	24	25	<1..1281
M358	ARHGAP8: Rho GTPase activating protein 8, variant 8	26	27	1..1386
M359	ARHGAP8: Rho GTPase activating protein 8, variant 9	28	29	<1..1059
OV5	BICD1: Bicaudal D homolog 1 (Drosophila)	30	31	82..3009
M431	BTG2: BTG family, member 2	32	33	72..548
M432	CADPS: Ca ²⁺ -dependent activator protein for secretion	34	35	240..4412
M609	CDH1: cadherin 1, type 1, E-cadherin (epithelial)	36	37	125..2773
M433	CDH6: cadherin 6, type 2, K-cadherin	38	39	327..2699
M434	CDKN2A: cyclin-dependent kinase inhibitor 2A	40	41	41..511
OV9	CGN: cingulin	42	43	152..3763
OV6	CHI3L1: cartilage glycoprotein-39	44	45	127..1278
M435	CKMT1: creatine kinase, mitochondrial 1 (ubiquitous)	46	47	164..1417
M604	CLDN10: claudin 10	48	49	36..772
OV10	CLDN16: claudin 16	50	51	69..986
M360	CLDN4: claudin 4	52	53	183..812
OV66	CP: ceruloplasmin (ferroxidase), variant 1	54	55	1..3210
OV7	CP: ceruloplasmin (ferroxidase), variant 2	56	57	<1..2561
OV8	CP: ceruloplasmin (ferroxidase), variant 3	58	59	1..3198
OV81	CP: ceruloplasmin (ferroxidase), variant 4	60	61	76..3348
M103	CRABP2: cellular retinoic acid-binding protein 2	62	63	138..554

OV40	DD96: Epithelial protein up-regulated in carcinoma, membrane associated protein 17	64	65	202..546
OV4	DEC2: basic helix-loop-helix protein	66	67	135..1583
M575	dehydrogenase	68	69	339..1364
M436	DLX5: distal-less homeo box 5	70	71	204..1073
OV12	EAB1: Eab1 protein	72	73	<1..1305
OV13	ESX protein	74	75	96..1211
OV67	EVI-1: Evi-1 protein, variant 1	76	77	250..2406
OV14	EVI-1: Evi-1 protein, variant 2	78	79	250..3405
OV15	EVI-1: Evi-1 protein, variant 3	80	81	250..2433
OV16	EVI-1: Evi-1 protein, variant 4	82	83	250..3378
M437	FLJ10546: hypothetical protein FLJ10546	84	85	28..1815
OV28	FLJ12799: hypothetical protein FLJ12799	86	87	39..797
M576	FLJ13710: hypothetical protein FLJ13710	88	89	96..1712
M438	FLJ13782: hypothetical protein FLJ13782	90	91	13..1890
OV29	FLJ20150: hypothetical protein FLJ20150	92	93	78..983
M439	FLJ20327: hypothetical protein FLJ20327	94	95	306..2186
M440	FLJ20758: hypothetical protein FLJ20758, variant 1	96	97	<2..1270
M441	FLJ20758: hypothetical protein FLJ20758, variant 2	98	99	<2..2095
M442	FLJ20758: hypothetical protein FLJ20758, variant 3	100	101	465..1307
M443	FLJ22252: likely ortholog of mouse SRY-box containing gene 17	102	103	205..1449
M444	FLJ22316: hypothetical protein FLJ22316	104	105	508..1206
M400	FLJ22418: hypothetical protein FLJ22418	106	107	71..919
M445	FLJ23499: hypothetical protein FLJ23499	108	109	21..473
OV17	FOLR1: folate receptor 1 (alpha), variant 1	110	111	139..912
OV18	FOLR1: folate receptor 1 (alpha), variant 2	112	111	211..984
OV19	FOLR1: folate receptor 1 (alpha), variant 3	113	111	46..819
OV20	FOLR1: folate receptor 1 (alpha), variant 4	114	111	437..1210
OV21	FOLR1: folate receptor 1 (alpha), variant 5	115	111	11..784
OV22	FOLR3: folate receptor 3 (gamma)	116	117	57..788
OV23	GPR39: G protein-coupled receptor 39	118	119	1..1362
M446	GPRC5B: G protein-coupled receptor, family C, group 5, member B	120	121	109..1320
OV24	G-protein coupled receptor	122	123	274..1236
M447	GRB7: growth factor receptor-bound protein 7	124	125	220..1818
OV11	HAIK1: type I intermediate filament cytokeratin	126	127	61..1329
M448	HOXB7: homeo box B7	128	129	100..753
M138	HSECP1: secretory protein, variant 1	130	131	27..863
M449	HSECP1: secretory protein, variant 2	132	133	136..768
M450	HSECP1: secretory protein, variant 3	134	135	202..933
M451	HSNFRK: HSNFRK protein	136	137	642..2939
OV26	hypothetical protein (1)	138	139	<1..1140
OV27	hypothetical protein (2)	140	141	242..1483
OV31	IFI30: interferon, gamma-inducible protein 30	142	143	41..952
OV58	IGF2: somatomedin A	144	145	553..1095

M452	IMP-2: IGF-II mRNA-binding protein 2	146	147	436..2106
M453	INDO: indoleamine-pyrrole 2, 3 dioxygenase	148	149	23..1234
OV73	IPT: tRNA isopentenylpyrophosphate transferase, variant 1	150	151	15..1418
M610	IPT: tRNA isopentenylpyrophosphate transferase, variant 2	152	153	15..1418
M454	ITGA3: integrin, alpha 3	154	155	74..3274
OV30	ITGB8: integrin, beta 8	156	157	681..2990
OV34	KIAA0762: KIAA0762 protein	158	159	<1..1875
M455	KIAA0869: KIAA0869 protein	160	161	<1..2668
OV35	KIAA1154: KIAA1154 protein	162	163	<1..677
OV36	KIAA1456: KIAA1456 protein	164	165	<366..1631
OV32	KLK10: kallikrein 10	166	167	82..912
OV33	KLK6: kallikrein 6	168	169	246..980
M456	KRT7: keratin 7, variant 1	170	171	57..1466
M611	KRT7: keratin 7, variant 2	172	173	54..1463
OV53	LC27: Putative integral membrane transporter	174	175	204..1055
OV37	LCN2: Lipocalin 2 (oncogene 24p3)	176	177	1..597
M457	LEFTB: left-right determination, factor B	178	179	71..1171
M559	LPHB: lipophilin B (uteroglobin family member), prostatein-like	180	181	64..336
OV38	LYST-interacting protein LIP6	182	183	11..586
OV39	MEIS1: MEIS1 protein	184	185	66..1238
M458	MGB2: mammaglobin 2	186	187	65..352
M459	MGC3184: similar to sialyltransferase 7 ((alpha-N-acetylneuraminy 2, 3-betagalactosyl-1, 3)-N-acetyl galactosaminide alpha-2, 6-sialyltransferase) E	188	189	176..1186
OV52	MMP7: Matrix metalloproteinase 7 (matrilysin, uterine)	190	191	28..831
OV68	MSLN: mesothelin, variant 1	192	193	88..2196
OV69	MSLN: mesothelin, variant 2	194	195	88..1980
OV70	MSLN: mesothelin, variant 3	196	197	88..1950
OV71	MSLN: mesothelin, variant 4	198	199	88..2172
OV72	MSLN: mesothelin, variant 5	200	201	88..1926
OV41	MSLN: mesothelin, variant 6	202	203	<1..>1195
OV42	MSLN: mesothelin, variant 7	204	205	85..1953
OV43	MSLN: mesothelin, variant 8	206	205	88..1956
OV44	MSLN: mesothelin, variant 9	207	208	89..1975
OV83	MSLN: mesothelin, variant 10	209	210	295..2187
OV45	MUC1: mucin 1	211	212	58..1605
M460	MUC16: mucin 16, variant 1	213	214	<1..5352
M461	MUC16: mucin 16, variant 2	215	216	25..3471
M612	MUC16: mucin 16, variant 3	215	217	<1..5673
M462	MYOM2: myomesin (M-protein)	218	219	49..4446
M463	NaPi-lib: sodium dependent phosphate transporter isoform	220	221	36..2105
M464	NME5: protein expressed in non-metastatic cells 5	222	223	15..653

OV47	NUFIP1: nuclear fragile X mental retardation protein interacting protein 1	224	225	1..1488
OV48	OPN-a: Secreted phosphoprotein-1 (osteopontin, bone sialoprotein)	226	227	1..942
OV49	OPN-b: Secreted phosphoprotein-1 (osteopontin, bone sialoprotein)	228	229	88..990
OV50	OPN-c: Secreted phosphoprotein-1 (osteopontin, bone sialoprotein)	230	231	1..861
M578	PAEP: progestagen-associated endometrial protein, variant 1	232	233	36..578
M579	PAEP: progestagen-associated endometrial protein, variant 2	234	233	36..578
M580	PAEP: progestagen-associated endometrial protein, variant 3	235	233	36..578
M581	PAEP: progestagen-associated endometrial protein, variant 4	236	233	36..578
M583	PAEP: progestagen-associated endometrial protein, variant 5	237	238	45..305
M582	PAEP: progestagen-associated endometrial protein, variant 6	239	240	45..521
M613	PAEP: progestagen-associated endometrial protein, variant 7	239	241	45..521
M465	PAX8: paired box gene 8, isoform 8A	242	243	11..1363
M466	PAX8: paired box gene 8, isoform 8B, variant 1	244	245	11..1174
M614	PAX8: paired box gene 8, isoform 8B, variant 2	244	246	11..1174
M467	PAX8: paired box gene 8, isoform 8C	247	248	161..1357
M468	PAX8: paired box gene 8, isoform 8D	249	250	161..1126
M469	PAX8: paired box gene 8, isoform 8E	251	252	161..1024
M470	PRAME: preferentially expressed antigen in melanoma	253	254	236..1765
M615	PRKCI: protein kinase C, iota	255	256	205..1968
M605	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 1	257	258	<1..3133
M606	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 2	259	258	<1..3133
M607	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 3	260	258	<1..3133
OV80	PRSS8: prostaticin	261	262	229..1260
OV51	PTGS1: prostaglandin-endoperoxide synthase 1	263	264	6..1805
M312	PTK9: protein tyrosine kinase 9	265	266	61..1113
OV54	pyruvate dehydrogenase complex component E2	267	268	49..>358
OV55	S100A1: S100 calcium-binding protein A1	269	270	114..398
M471	S100A11: S100 calcium-binding protein A11 (calgizzarin)	271	272	121..438
M68	S100A2: S100 calcium-binding protein A2	273	274	41..334
M585	S100A6: S100 calcium-binding protein A6 (calcyclin)	275	276	103..375

OV57	SCNN1A: sodium channel, nonvoltage-gated 1 alpha, variant 1	277	278	100..2109
OV85	SCNN1A: sodium channel, nonvoltage-gated 1 alpha, variant 2	279	280	96..2105
M472	secreted protein (HETKL27)	281	282	88..618
M473	SEMA3A: sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3A	283	284	16..2331
OV2	SERPINA1: alpha-1 antitrypsin	285	286	35..1291
M474	Similar to hypothetical protein, MGC: 7199	287	288	173..1053
M586	Similar to proteasome (prosome, macropain) subunit, alpha type, 3	289	290	45..791
M587	Similar to zinc finger protein 136	291	292	139..1524
M475	SLPI: secretory leukocyte protease inhibitor (antileukoproteinase), variant 1	293	294	271..447
M185	SLPI: secretory leukocyte protease inhibitor (antileukoproteinase), variant 2	295	296	19..417
OV60	SNCG: synuclein, gamma	297	298	49..432
OV59	SORL1: sortilin-related receptor	299	300	198..6842
OV56	SPINT2: serine protease inhibitor, Kunitz type, 2, variant 1	301	302	301..1059
OV84	SPINT2: serine protease inhibitor, Kunitz type, 2, variant 2	303	304	332..919
OV65	SPON1: VSGP/F-spondin, variant 1	305	306	25..2448
M593	SPON1: VSGP/F-spondin, variant 2	307	308	180..2984
M594	SPON1: VSGP/F-spondin, variant 3	309	310	180..2687
OV82	ST14: matriptase	311	312	209..2557
M476	TACSTD2: tumor-associated calcium signal transducer 2	313	314	616..1587
M588	TFPI2: tissue factor pathway inhibitor 2	315	316	57..764
OV86	TMPRSS4: transmembrane protease, serine 4	317	318	310..1623
OV74	TPH: tryptophan hydroxylase, variant 1	319	320	1..1335
OV75	TPH: tryptophan hydroxylase, variant 2	321	322	1..1401
M327	TSPAN-1: Tetraspan NET-1 protein, variant 1	323	324	124..900
M328	TSPAN-1: Tetraspan NET-1 protein, variant 2	325	326	1..726
OV46	TTID: myotilin	327	328	281..1777
M589	UCH2: Ubiquitin carboxyl-terminal hydrolases family 2	329	330	551..2940
OV63	unnamed gene (1)	331	332	71..919
OV64	unnamed gene (2)	333	334	28..804
OV76	unnamed gene (3)	335	336	69..773
OV77	unnamed gene (4)	337	338	223..1284
OV78	unnamed gene (5), variant 1	339	340	84..2450
M616	unnamed gene (5), variant 2	341	342	84..2450
OV79	unnamed gene (6)	343	344	69..392
OV87	unnamed gene (7)	345	346	509..2428
OV88	unnamed gene (8)	347	348	71..919
M477	unnamed gene (9), variant 1	349	350	246..992
M617	unnamed gene (9), variant 2	349	351	246..992
M478	unnamed gene (9), variant 3	352	353	246..1004

M479	unnamed gene (9), variant 4	354	355	246..1049
M590	unnamed gene (10), variant 1	356	357	21..404
M591	unnamed gene (10), variant 2	358	357	21..404
M592	unnamed gene (10), variant 3	359	357	21..404
OV25	WFDC2: Epididymis-specific, whey-acidic protein type, four-disulfide core; putative ovarian carcinoma marker	360	361	28..405
M480	XRCC5, KU80: ATP-dependant DNA helicase II	362	363	34..2232

TABLE 2

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M354	ARHGAP8: Rho GTPase activating protein 8, variant 3	17	18	1..2256
M608	ARHGAP8: Rho GTPase activating protein 8, variant 4	17	19	1..2157
M355	ARHGAP8: Rho GTPase activating protein 8, variant 5	20	21	<1..1314
M356	ARHGAP8: Rho GTPase activating protein 8, variant 6	22	23	1..1902
M357	ARHGAP8: Rho GTPase activating protein 8, variant 7	24	25	<1..1281
M358	ARHGAP8: Rho GTPase activating protein 8, variant 8	26	27	1..1386
M359	ARHGAP8: Rho GTPase activating protein 8, variant 9	28	29	<1..1059
OV66	CP: ceruloplasmin (ferroxidase), variant 1	54	55	1..3210
OV81	CP: ceruloplasmin (ferroxidase), variant 4	60	61	76..3348
M575	dehydrogenase	68	69	339..1364
OV67	EVI-1: Evi-1 protein, variant 1	76	77	250..2406
M440	FLJ20758: hypothetical protein FLJ20758, variant 1	96	97	<2..1270
M441	FLJ20758: hypothetical protein FLJ20758, variant 2	98	99	<2..2095
M449	HSECP1: secretory protein, variant 2	132	133	136..768
M450	HSECP1: secretory protein, variant 3	134	135	202..933
OV73	IPT: tRNA isopentenylpyrophosphate transferase, variant 1	150	151	15..1418
M610	IPT: tRNA isopentenylpyrophosphate transferase, variant 2	152	153	15..1418
M611	KRT7: keratin 7, variant 2	172	173	54..1463
OV68	MSLN: mesothelin, variant 1	192	193	88..2196
OV69	MSLN: mesothelin, variant 2	194	195	88..1980
OV70	MSLN: mesothelin, variant 3	196	197	88..1950
OV71	MSLN: mesothelin, variant 4	198	199	88..2172
OV72	MSLN: mesothelin, variant 5	200	201	88..1926
OV83	MSLN: mesothelin, variant 10	209	210	295..2187
M460	MUC16: mucin 16, variant 1	213	214	<1..5352
M583	PAEP: progesterone-associated endometrial protein, variant 5	237	238	45..305

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M613	PAEP: progestagen-associated endometrial protein, variant 7	239	241	45..521
M614	PAX8: paired box gene 8, isoform 8B, variant 2	244	246	11..1174
M605	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 1	257	258	<1..3133
M606	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 2	259	258	<1..3133
M607	PRP4: serine/threonine-protein kinase PRP4 homolog, variant 3	260	258	<1..3133
OV85	SCNN1A: sodium channel, nonvoltage-gated 1 alpha, variant 2	279	280	96..2105
M475	SLPI: secretory leukocyte protease inhibitor (antileukoproteinase), variant 1	293	294	271..447
OV84	SPINT2: serine protease inhibitor, Kunitz type, 2, variant 2	303	304	332..919
M593	SPON1: VSGP/F-spondin, variant 2	307	308	180..2984
M594	SPON1: VSGP/F-spondin, variant 3	309	310	180..2687
OV82	ST14: matriptase	311	312	209..2557
OV86	TMPRSS4: transmembrane protease, serine 4	317	318	310..1623
OV74	TPH: tryptophan hydroxylase, variant 1	319	320	1..1335
OV75	TPH: tryptophan hydroxylase, variant 2	321	322	1..1401
M327	TSPAN-1: Tetraspan NET-1 protein, variant 1	323	324	124..900
M589	UCH2: Ubiquitin carboxyl-terminal hydrolases family 2	329	330	551..2940
OV76	unnamed gene (3)	335	336	69..773
OV77	unnamed gene (4)	337	338	223..1284
OV78	unnamed gene (5), variant 1	339	340	84..2450
M616	unnamed gene (5), variant 2	341	342	84..2450
OV79	unnamed gene (6)	343	344	69..392
OV87	unnamed gene (7)	345	346	509..2428
OV88	unnamed gene (8)	347	348	71..919
M477	unnamed gene (9), variant 1	349	350	246..992
M617	unnamed gene (9), variant 2	349	351	246..992
M478	unnamed gene (9), variant 3	352	353	246..1004
M479	unnamed gene (9), variant 4	354	355	246..1049

TABLE 3

Marker	Gene Name	SEQ ID NO (nts)	SEQ ID NO (AAs)	CDS
M604	CLDN10: claudin 10	48	49	36..772
OV14	EVI-1: Evi-1 protein, variant 2	78	79	250..3405
OV15	EVI-1: Evi-1 protein, variant 3	80	81	250..2433
OV16	EVI-1: Evi-1 protein, variant 4	82	83	250..3378
M576	FLJ13710: hypothetical protein FLJ13710	88	89	96..1712
M444	FLJ22316: hypothetical protein FLJ22316	104	105	508..1206
OV30	ITGB8: integrin, beta 8	156	157	681..2990
OV43	MSLN: mesothelin, variant 8	206	205	88..1956

M581	PAEP: progestagen-associated endometrial protein, variant 4	236	233	36..578
M582	PAEP: progestagen-associated endometrial protein, variant 6	239	240	45..521
M466	PAX8: paired box gene 8, isoform 8B, variant 1	244	245	11..1174
M467	PAX8: paired box gene 8, isoform 8C	247	248	161..1357
M468	PAX8: paired box gene 8, isoform 8D	249	250	161..1126
M469	PAX8: paired box gene 8, isoform 8E	251	252	161..1024
OV2	SERPINA1: alpha-1 antitrypsin	285	286	35..1291
M474	Similar to hypothetical protein, MGC: 7199	287	288	173..1053
M590	unnamed gene (10), variant 1	356	357	21..404
M591	unnamed gene (10), variant 2	358	357	21..404
M592	unnamed gene (10), variant 3	359	357	21..404

Definitions

As used herein, each of the following terms has the meaning associated with it in this section.

The articles "a" and "an" are used herein to refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

A "marker" is a gene whose altered level of expression in a tissue or cell from its expression level in normal or healthy tissue or cell is associated with a disease state, such as cancer. A "marker nucleic acid" is a nucleic acid (*e.g.*, mRNA, cDNA) encoded by or corresponding to a marker of the invention. Such marker nucleic acids can be DNA (*e.g.*, cDNA) comprising the sequences listed in Table 1 or the complement of such sequences. The marker nucleic acids also can be RNA comprising the sequences listed in Table 1 or the complement of such sequence, wherein all thymidine residues are replaced with uridine residues. A "marker protein" is a protein encoded by or corresponding to a marker of the invention. A marker protein comprises the sequence of any of the sequences listed in Table 1. The terms "protein" and "polypeptide" are used interchangeably.

The term "probe" refers to any molecule which is capable of selectively binding to a specifically intended target molecule, for example, a nucleotide transcript or protein encoded by or corresponding to a marker. Probes can be either synthesized by one skilled in the art, or derived from appropriate biological preparations. For purposes of detection of the target molecule, probes may be specifically designed to be

labeled, as described herein. Examples of molecules that can be utilized as probes include, but are not limited to, RNA, DNA, proteins, antibodies, and organic molecules.

An "ovary-associated" body fluid is a fluid which, when in the body of a patient, contacts or passes through ovarian cells or into which cells or proteins shed from ovarian cells *e.g.*, ovarian epithelium, are capable of passing. Exemplary ovary-associated body fluids include blood fluids, lymph, ascites, gynecological fluids, cystic fluid, urine, and fluids collected by peritoneal rinsing.

The "normal" level of expression of a marker is the level of expression of the marker in ovarian cells of a human subject or patient not afflicted with ovarian cancer

An "over-expression" or "significantly higher level of expression" of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least twice, and more preferably three, four, five or ten times the expression level of the marker in a control sample (*e.g.*, sample from a healthy subjects not having the marker associated disease) and preferably, the average expression level of the marker in several control samples.

As used herein, the term "promoter/regulatory sequence" means a nucleic acid sequence which is required for expression of a gene product operably linked to the promoter/regulatory sequence. In some instances, this sequence may be the core promoter sequence and in other instances, this sequence may also include an enhancer sequence and other regulatory elements which are required for expression of the gene product. The promoter/regulatory sequence may, for example, be one which expresses the gene product in a tissue-specific manner.

A "constitutive" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell under most or all physiological conditions of the cell.

An "inducible" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only when an inducer which corresponds to the promoter is present in the cell.

A "tissue-specific" promoter is a nucleotide sequence which, when operably linked with a polynucleotide which encodes or specifies a gene product, causes the gene product to be produced in a living human cell substantially only if the cell is a cell of the tissue type corresponding to the promoter.

5 A "transcribed polynucleotide" or "nucleotide transcript" is a polynucleotide (*e.g.* an mRNA, hnRNA, a cDNA, or an analog of such RNA or cDNA) which is complementary to or homologous with all or a portion of a mature mRNA made by transcription of a marker of the invention and normal post-transcriptional processing (*e.g.* splicing), if any, of the RNA transcript, and reverse transcription of the
10 RNA transcript.

"Complementary" refers to the broad concept of sequence complementarity between regions of two nucleic acid strands or between two regions of the same nucleic acid strand. It is known that an adenine residue of a first nucleic acid region is capable of forming specific hydrogen bonds ("base pairing") with a residue of
15 a second nucleic acid region which is antiparallel to the first region if the residue is thymine or uracil. Similarly, it is known that a cytosine residue of a first nucleic acid strand is capable of base pairing with a residue of a second nucleic acid strand which is antiparallel to the first strand if the residue is guanine. A first region of a nucleic acid is complementary to a second region of the same or a different nucleic acid if, when the
20 two regions are arranged in an antiparallel fashion, at least one nucleotide residue of the first region is capable of base pairing with a residue of the second region. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, when the first and second portions are arranged in an antiparallel fashion, at least about 50%, and preferably at least about 75%, at least about 90%, or at
25 least about 95% of the nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion. More preferably, all nucleotide residues of the first portion are capable of base pairing with nucleotide residues in the second portion.

"Homologous" as used herein, refers to nucleotide sequence similarity
30 between two regions of the same nucleic acid strand or between regions of two different nucleic acid strands. When a nucleotide residue position in both regions is occupied by the same nucleotide residue, then the regions are homologous at that position. A first

region is homologous to a second region if at least one nucleotide residue position of each region is occupied by the same residue. Homology between two regions is expressed in terms of the proportion of nucleotide residue positions of the two regions that are occupied by the same nucleotide residue. By way of example, a region having
5 the nucleotide sequence 5'-ATTGCC-3' and a region having the nucleotide sequence 5'-TATGGC-3' share 50% homology. Preferably, the first region comprises a first portion and the second region comprises a second portion, whereby, at least about 50%, and preferably at least about 75%, at least about 90%, or at least about 95% of the nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.
10 More preferably, all nucleotide residue positions of each of the portions are occupied by the same nucleotide residue.

A molecule is "fixed" or "affixed" to a substrate if it is covalently or non-covalently associated with the substrate such the substrate can be rinsed with a fluid (*e.g.* standard saline citrate, pH 7.4) without a substantial fraction of the molecule
15 dissociating from the substrate.

As used herein, a "naturally-occurring" nucleic acid molecule refers to an RNA or DNA molecule having a nucleotide sequence that occurs in an organism found in nature.

A cancer is "inhibited" if at least one symptom of the cancer is alleviated, terminated, slowed, or prevented. As used herein, ovarian cancer is also "inhibited" if
20 recurrence or metastasis of the cancer is reduced, slowed, delayed, or prevented.

A kit is any manufacture (*e.g.* a package or container) comprising at least one reagent, *e.g.* a probe, for specifically detecting the expression of a marker of the invention. The kit may be promoted, distributed, or sold as a unit for performing the
25 methods of the present invention.

"Proteins of the invention" encompass marker proteins and their fragments; variant marker proteins and their fragments; peptides and polypeptides comprising an at least 15 amino acid segment of a marker or variant marker protein; and fusion proteins comprising a marker or variant marker protein, or an at least 15 amino
30 acid segment of a marker or variant marker protein.

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Unless otherwise specified herewithin, the terms “antibody” and “antibodies” broadly encompass naturally-occurring forms of antibodies (*e.g.*, IgG, IgA, IgM, IgE) and recombinant antibodies such as single-chain antibodies, chimeric and humanized antibodies and multi-specific antibodies, as well as fragments and derivatives of all of the foregoing, which fragments and derivatives have at least an antigenic binding site. Antibody derivatives may comprise a protein or chemical moiety conjugated to an antibody moiety.

Description

The present invention is based, in part, on newly identified markers which are over-expressed in ovarian cancer cells as compared to their expression in normal (*i.e.* non-cancerous) ovarian cells. The enhanced expression of one or more of these markers in ovarian cells is herein correlated with the cancerous state of the tissue. The invention provides compositions, kits, and methods for assessing the cancerous state of ovarian cells (*e.g.* cells obtained from a human, cultured human cells, archived or preserved human cells and *in vivo* cells) as well as treating patients afflicted with ovarian cancer.

The compositions, kits, and methods of the invention have the following uses, among others:

- 1) assessing whether a patient is afflicted with ovarian cancer;
- 2) assessing the stage of ovarian cancer in a human patient;
- 3) assessing the grade of ovarian cancer in a patient;
- 4) assessing the benign or malignant nature of ovarian cancer in a patient;
- 5) assessing the metastatic potential of ovarian cancer in a patient;
- 6) assessing the histological type of neoplasm (*e.g.* serous, mucinous, endometrioid, or clear cell neoplasm) associated with ovarian cancer in a patient;
- 7) making antibodies, antibody fragments or antibody derivatives that are useful for treating ovarian cancer and/or assessing whether a patient is afflicted with ovarian cancer;

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- 8) assessing the presence of ovarian cancer cells;
- 9) assessing the efficacy of one or more test compounds for inhibiting ovarian cancer in a patient;
- 10) assessing the efficacy of a therapy for inhibiting ovarian cancer in a patient;
- 11) monitoring the progression of ovarian cancer in a patient;
- 12) selecting a composition or therapy for inhibiting ovarian cancer in a patient;
- 13) treating a patient afflicted with ovarian cancer;
- 14) inhibiting ovarian cancer in a patient;
- 15) assessing the ovarian carcinogenic potential of a test compound; and
- 16) preventing the onset of ovarian cancer in a patient at risk for developing ovarian cancer.

The invention thus includes a method of assessing whether a patient is afflicted with ovarian cancer which includes assessing whether the patient has pre-metastasized ovarian cancer. This method comprises comparing the level of expression of a marker of the invention (listed in Table 1) in a patient sample and the normal level of expression of the marker in a control, *e.g.*, a non-ovarian cancer sample. A significantly higher level of expression of the marker in the patient sample as compared to the normal level is an indication that the patient is afflicted with ovarian cancer.

Gene delivery vehicles, host cells and compositions (all described herein) containing nucleic acids comprising the entirety, or a segment of 15 or more nucleotides, of any of the sequences listed in Tables 1-3 or the complement of such sequences, and polypeptides comprising the entirety, or a segment of 10 or more amino acids, of any of the sequences listed in Tables 1-3 are also provided by this invention.

As described herein, ovarian cancer in patients is associated with an increased level of expression of one or more markers of the invention. While, as discussed above, some of these changes in expression level result from occurrence of the ovarian cancer, others of these changes induce, maintain, and promote the cancerous state of ovarian cancer cells. Thus, ovarian cancer characterized by an increase in the level of expression of one or more markers of the invention can be inhibited by reducing

and/or interfering with the expression of the markers and/or function of the proteins encoded by those markers.

Expression of a marker of the invention can be inhibited in a number of ways generally known in the art. For example, an antisense oligonucleotide can be provided to the ovarian cancer cells in order to inhibit transcription, translation, or both, of the marker(s). Alternately, a polynucleotide encoding an antibody, an antibody derivative, or an antibody fragment which specifically binds a marker protein, and operably linked with an appropriate promoter/regulator region, can be provided to the cell in order to generate intracellular antibodies which will inhibit the function or activity of the protein. The expression and/or function of a marker may also be inhibited by treating the ovarian cancer cell with an antibody, antibody derivative or antibody fragment that specifically binds a marker protein. Using the methods described herein, a variety of molecules, particularly including molecules sufficiently small that they are able to cross the cell membrane, can be screened in order to identify molecules which inhibit expression of a marker or inhibit the function of a marker protein. The compound so identified can be provided to the patient in order to inhibit ovarian cancer cells of the patient.

Any marker or combination of markers of the invention, as well as any known markers in combination with the markers of the invention, may be used in the compositions, kits, and methods of the present invention. In general, it is preferable to use markers for which the difference between the level of expression of the marker in ovarian cancer cells and the level of expression of the same marker in normal ovarian cells is as great as possible. Although this difference can be as small as the limit of detection of the method for assessing expression of the marker, it is preferred that the difference be at least greater than the standard error of the assessment method, and preferably a difference of at least 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 15-, 20-, 25-, 100-, 500-, 1000-fold or greater than the level of expression of the same marker in normal ovarian tissue.

It is recognized that certain marker proteins are secreted from ovarian cells (*i.e.* one or both of normal and cancerous cells) to the extracellular space surrounding the cells. These markers are preferably used in certain embodiments of the compositions, kits, and methods of the invention, owing to the fact that the such marker

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proteins can be detected in an ovary-associated body fluid sample, which may be more easily collected from a human patient than a tissue biopsy sample. In addition, preferred *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein. For example, the antibody can be labeled
5 with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

It is a simple matter for the skilled artisan to determine whether any particular marker protein is a secreted protein. In order to make this determination, the marker protein is expressed in, for example, a mammalian cell, preferably a human
10 ovarian cell line, extracellular fluid is collected, and the presence or absence of the protein in the extracellular fluid is assessed (*e.g.* using a labeled antibody which binds specifically with the protein).

The following is an example of a method which can be used to detect secretion of a protein. About 8×10^5 293T cells are incubated at 37°C in wells
15 containing growth medium (Dulbecco's modified Eagle's medium {DMEM} supplemented with 10% fetal bovine serum) under a 5% (v/v) CO₂, 95% air atmosphere to about 60-70% confluence. The cells are then transfected using a standard transfection mixture comprising 2 micrograms of DNA comprising an expression vector encoding the protein and 10 microliters of LipofectAMINE™ (GIBCO/BRL Catalog no. 18342-
20 012) per well. The transfection mixture is maintained for about 5 hours, and then replaced with fresh growth medium and maintained in an air atmosphere. Each well is gently rinsed twice with DMEM which does not contain methionine or cysteine (DMEM-MC; ICN Catalog no. 16-424- 54). About 1 milliliter of DMEM-MC and about 50 microcuries of Trans-³⁵S™ reagent (ICN Catalog no. 51006) are added to each
25 well. The wells are maintained under the 5% CO₂ atmosphere described above and incubated at 37°C for a selected period. Following incubation, 150 microliters of conditioned medium is removed and centrifuged to remove floating cells and debris. The presence of the protein in the supernatant is an indication that the protein is secreted.

Examples of ovary-associated body fluids include blood fluids (*e.g.* whole blood, blood serum, blood having platelets removed therefrom, etc.), lymph, ascitic fluids, gynecological fluids (*e.g.* ovarian, fallopian, and uterine secretions, menses, vaginal douching fluids, fluids used to rinse ovarian cell samples, etc.), cystic
5 fluid, urine, and fluids collected by peritoneal rinsing (*e.g.* fluids applied and collected during laparoscopy or fluids instilled into and withdrawn from the peritoneal cavity of a human patient). In these embodiments, the level of expression of the marker can be assessed by assessing the amount (*e.g.* absolute amount or concentration) of the marker protein in an ovary-associated body fluid obtained from a patient. The fluid can, of
10 course, be subjected to a variety of well-known post-collection preparative and storage techniques (*e.g.* storage, freezing, ultrafiltration, concentration, evaporation, centrifugation, etc.) prior to assessing the amount of the marker in the fluid.

Many ovary-associated body fluids (*i.e.* usually excluding urine) can have ovarian cells, *e.g.* ovarian epithelium, therein, particularly when the ovarian cells
15 are cancerous, and, more particularly, when the ovarian cancer is metastasizing. Cell-containing fluids which can contain ovarian cancer cells include, but are not limited to, peritoneal ascites, fluids collected by peritoneal rinsing, fluids collected by uterine rinsing, uterine fluids such as uterine exudate and menses, pleural fluid, and ovarian exudates. Thus, the compositions, kits, and methods of the invention can be used to
20 detect expression of marker proteins having at least one portion which is displayed on the surface of cells which express it. It is a simple matter for the skilled artisan to determine whether a marker protein, or a portion thereof, is exposed on the cell surface. For example, immunological methods may be used to detect such proteins on whole cells, or well known computer-based sequence analysis methods (*e.g.* the SIGNALP
25 program; Nielsen *et al.*, 1997, *Protein Engineering* 10:1-6) may be used to predict the presence of at least one extracellular domain (*i.e.* including both secreted proteins and proteins having at least one cell-surface domain). Expression of a marker protein having at least one portion which is displayed on the surface of a cell which expresses it may be detected without necessarily lysing the cell (*e.g.* using a labeled antibody which binds
30 specifically with a cell-surface domain of the protein).

Expression of a marker of the invention may be assessed by any of a wide variety of well known methods for detecting expression of a transcribed nucleic acid or protein. Non-limiting examples of such methods include immunological methods for detection of secreted, cell-surface, cytoplasmic, or nuclear proteins, protein
5 purification methods, protein function or activity assays, nucleic acid hybridization methods, nucleic acid reverse transcription methods, and nucleic acid amplification methods.

In a preferred embodiment, expression of a marker is assessed using an antibody (*e.g.* a radio-labeled, chromophore-labeled, fluorophore-labeled, or enzyme-
10 labeled antibody), an antibody derivative (*e.g.* an antibody conjugated with a substrate or with the protein or ligand of a protein-ligand pair {*e.g.* biotin-streptavidin}), or an antibody fragment (*e.g.* a single-chain antibody, an isolated antibody hypervariable domain, etc.) or derivative which binds specifically with a marker protein or fragment thereof, including a marker protein which has undergone all or a portion of its normal
15 post-translational modification.

In another preferred embodiment, expression of a marker is assessed by preparing mRNA/cDNA (*i.e.* a transcribed polynucleotide) from cells in a patient sample, and by hybridizing the mRNA/cDNA with a reference polynucleotide which is a complement of a marker nucleic acid, or a fragment thereof. cDNA can, optionally, be
20 amplified using any of a variety of polymerase chain reaction methods prior to hybridization with the reference polynucleotide; preferably, it is not amplified. Expression of one or more markers can likewise be detected using quantitative PCR to assess the level of expression of the marker(s). Alternatively, any of the many known methods of detecting mutations or variants (*e.g.* single nucleotide polymorphisms,
25 deletions, etc.) of a marker of the invention may be used to detect occurrence of a marker in a patient.

In a related embodiment, a mixture of transcribed polynucleotides obtained from the sample is contacted with a substrate having fixed thereto a polynucleotide complementary to or homologous with at least a portion (*e.g.* at least 7,
30 10, 15, 20, 25, 30, 40, 50, 100, 500, or more nucleotide residues) of a marker nucleic acid. If polynucleotides complementary to or homologous with several marker nucleic acids are differentially detectable on the substrate (*e.g.* detectable using different

chromophores or fluorophores, or fixed to different selected positions), then the levels of expression of a plurality of markers can be assessed simultaneously using a single substrate (*e.g.* a "gene chip" microarray of polynucleotides fixed at selected positions). When a method of assessing marker expression is used which involves hybridization of
5 one nucleic acid with another, it is preferred that the hybridization be performed under stringent hybridization conditions.

Because the compositions, kits, and methods of the invention rely on detection of a difference in expression levels of one or more markers of the invention, it is preferable that the level of expression of the marker is significantly greater than the
10 minimum detection limit of the method used to assess expression in at least one of normal ovarian cells and cancerous ovarian cells.

It is understood that by routine screening of additional patient samples using one or more of the markers of the invention, it will be realized that certain of the markers are over-expressed in cancers of various types, including specific ovarian
15 cancers, as well as other cancers such as breast cancer, cervical cancer, etc. For example, it will be confirmed that some of the markers of the invention are over-expressed in most (*i.e.* 50% or more) or substantially all (*i.e.* 80% or more) of ovarian cancer. Furthermore, it will be confirmed that certain of the markers of the invention are associated with ovarian cancer of various stages (*i.e.* stage I, II, III, and IV ovarian
20 cancers, as well as subclassifications IA, IB, IC, IIA, IIB, IIC, IIIA, IIIB, and IIIC, using the FIGO Stage Grouping system for primary carcinoma of the ovary; 1987, *Am. J. Obstet. Gynecol.* 156:236), of various histologic subtypes (*e.g.* serous, mucinous, endometrioid, and clear cell subtypes, as well as subclassifications and alternate classifications adenocarcinoma, papillary adenocarcinoma, papillary
25 cystadenocarcinoma, surface papillary carcinoma, malignant adenofibroma, cystadenofibroma, adenocarcinoma, cystadenocarcinoma, adenoacanthoma, endometrioid stromal sarcoma, mesodermal (Müllerian) mixed tumor, mesonephroid tumor, malignant carcinoma, Brenner tumor, mixed epithelial tumor, and undifferentiated carcinoma, using the WHO/FIGO system for classification of malignant
30 ovarian tumors; Scully, *Atlas of Tumor Pathology*, 3d series, Washington DC), and various grades (*i.e.* grade I {well differentiated} , grade II {moderately well differentiated}, and grade III {poorly differentiated from surrounding normal tissue}).

In addition, as a greater number of patient samples are assessed for expression of the markers of the invention and the outcomes of the individual patients from whom the samples were obtained are correlated, it will also be confirmed that increased expression of certain of the markers of the invention are strongly correlated with malignant cancers and that increased expression of other markers of the invention are strongly correlated with benign tumors. The compositions, kits, and methods of the invention are thus useful for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of ovarian cancer in patients. In addition, these compositions, kits, and methods can be used to detect and differentiate epithelial, stromal, and germ cell ovarian cancers.

When the compositions, kits, and methods of the invention are used for characterizing one or more of the stage, grade, histological type, and benign/malignant nature of ovarian cancer in a patient, it is preferred that the marker or panel of markers of the invention is selected such that a positive result is obtained in at least about 20%, and preferably at least about 40%, 60%, or 80%, and more preferably in substantially all patients afflicted with an ovarian cancer of the corresponding stage, grade, histological type, or benign/malignant nature. Preferably, the marker or panel of markers of the invention is selected such that a PPV of greater than about 10% is obtained for the general population (more preferably coupled with an assay specificity greater than 99.5%).

When a plurality of markers of the invention are used in the compositions, kits, and methods of the invention, the level of expression of each marker in a patient sample can be compared with the normal level of expression of each of the plurality of markers in non-cancerous samples of the same type, either in a single reaction mixture (*i.e.* using reagents, such as different fluorescent probes, for each marker) or in individual reaction mixtures corresponding to one or more of the markers. In one embodiment, a significantly increased level of expression of more than one of the plurality of markers in the sample, relative to the corresponding normal levels, is an indication that the patient is afflicted with ovarian cancer. When a plurality of markers is used, it is preferred that 2, 3, 4, 5, 8, 10, 12, 15, 20, 30, or 50 or more individual markers be used, wherein fewer markers are preferred.

In order to maximize the sensitivity of the compositions, kits, and methods of the invention (*i.e.* by interference attributable to cells of non-ovarian origin in a patient sample), it is preferable that the marker of the invention used therein be a marker which has a restricted tissue distribution, *e.g.*, normally not expressed in a non-epithelial tissue, and more preferably a marker which is normally not expressed in a non-ovarian tissue.

Only a small number of markers are known to be associated with ovarian cancers (*e.g.* *AKT2*, *Ki-RAS*, *ERBB2*, *c-MYC*, *RBI*, and *TP53*; Lynch, *supra*). These markers are not, of course, included among the markers of the invention, although they may be used together with one or more markers of the invention in a panel of markers, for example. It is well known that certain types of genes, such as oncogenes, tumor suppressor genes, growth factor-like genes, protease-like genes, and protein kinase-like genes are often involved with development of cancers of various types. Thus, among the markers of the invention, use of those which correspond to proteins which resemble proteins encoded by known oncogenes and tumor suppressor genes, and those which correspond to proteins which resemble growth factors, proteases, and protein kinases are preferred.

It is recognized that the compositions, kits, and methods of the invention will be of particular utility to patients having an enhanced risk of developing ovarian cancer and their medical advisors. Patients recognized as having an enhanced risk of developing ovarian cancer include, for example, patients having a familial history of ovarian cancer, patients identified as having a mutant oncogene (*i.e.* at least one allele), and patients of advancing age (*i.e.* women older than about 50 or 60 years).

The level of expression of a marker in normal (*i.e.* non-cancerous) human ovarian tissue can be assessed in a variety of ways. In one embodiment, this normal level of expression is assessed by assessing the level of expression of the marker in a portion of ovarian cells which appears to be non-cancerous and by comparing this normal level of expression with the level of expression in a portion of the ovarian cells which is suspected of being cancerous. For example, when laparoscopy or other medical procedure, reveals the presence of a lump on one portion of a patient's ovary, but not on another portion of the same ovary or on the other ovary, the normal level of expression of a marker may be assessed using one or both or the non-affected ovary and

a non-affected portion of the affected ovary, and this normal level of expression may be compared with the level of expression of the same marker in an affected portion (*i.e.* the lump) of the affected ovary. Alternately, and particularly as further information becomes available as a result of routine performance of the methods described herein, population-average values for normal expression of the markers of the invention may be used. In other embodiments, the 'normal' level of expression of a marker may be determined by assessing expression of the marker in a patient sample obtained from a non-cancer-afflicted patient, from a patient sample obtained from a patient before the suspected onset of ovarian cancer in the patient, from archived patient samples, and the like.

The invention includes compositions, kits, and methods for assessing the presence of ovarian cancer cells in a sample (*e.g.* an archived tissue sample or a sample obtained from a patient). These compositions, kits, and methods are substantially the same as those described above, except that, where necessary, the compositions, kits, and methods are adapted for use with samples other than patient samples. For example, when the sample to be used is a paraffinized, archived human tissue sample, it can be necessary to adjust the ratio of compounds in the compositions of the invention, in the kits of the invention, or the methods used to assess levels of marker expression in the sample. Such methods are well known in the art and within the skill of the ordinary artisan.

The invention includes a kit for assessing the presence of ovarian cancer cells (*e.g.* in a sample such as a patient sample). The kit comprises a plurality of reagents, each of which is capable of binding specifically with a marker nucleic acid or protein. Suitable reagents for binding with a marker protein include antibodies, antibody derivatives, antibody fragments, and the like. Suitable reagents for binding with a marker nucleic acid (*e.g.* a genomic DNA, an mRNA, a spliced mRNA, a cDNA, or the like) include complementary nucleic acids. For example, the nucleic acid reagents may include oligonucleotides (labeled or non-labeled) fixed to a substrate, labeled oligonucleotides not bound with a substrate, pairs of PCR primers, molecular beacon probes, and the like.

The kit of the invention may optionally comprise additional components useful for performing the methods of the invention. By way of example, the kit may comprise fluids (*e.g.* SSC buffer) suitable for annealing complementary nucleic acids or for binding an antibody with a protein with which it specifically binds, one or more
5 sample compartments, an instructional material which describes performance of a method of the invention, a sample of normal ovarian cells, a sample of ovarian cancer cells, and the like.

The invention also includes a method of making an isolated hybridoma which produces an antibody useful for assessing whether patient is afflicted with an
10 ovarian cancer. In this method, a protein or peptide comprising the entirety or a segment of a marker protein is synthesized or isolated (*e.g.* by purification from a cell in which it is expressed or by transcription and translation of a nucleic acid encoding the protein or peptide *in vivo* or *in vitro* using known methods). A vertebrate, preferably a mammal such as a mouse, rat, rabbit, or sheep, is immunized using the protein or peptide. The
15 vertebrate may optionally (and preferably) be immunized at least one additional time with the protein or peptide, so that the vertebrate exhibits a robust immune response to the protein or peptide. Splenocytes are isolated from the immunized vertebrate and fused with an immortalized cell line to form hybridomas, using any of a variety of methods well known in the art. Hybridomas formed in this manner are then screened
20 using standard methods to identify one or more hybridomas which produce an antibody which specifically binds with the marker protein or a fragment thereof. The invention also includes hybridomas made by this method and antibodies made using such hybridomas.

The invention also includes a method of assessing the efficacy of a test
25 compound for inhibiting ovarian cancer cells. As described above, differences in the level of expression of the markers of the invention correlate with the cancerous state of ovarian cells. Although it is recognized that changes in the levels of expression of certain of the markers of the invention likely result from the cancerous state of ovarian cells, it is likewise recognized that changes in the levels of expression of other of the
30 markers of the invention induce, maintain, and promote the cancerous state of those cells. Thus, compounds which inhibit an ovarian cancer in a patient will cause the level of expression of one or more of the markers of the invention to change to a level nearer

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the normal level of expression for that marker (*i.e.* the level of expression for the marker in non-cancerous ovarian cells).

This method thus comprises comparing expression of a marker in a first ovarian cell sample and maintained in the presence of the test compound and expression
5 of the marker in a second ovarian cell sample and maintained in the absence of the test compound. A significantly reduced expression of a marker of the invention in the presence of the test compound is an indication that the test compound inhibits ovarian cancer. The ovarian cell samples may, for example, be aliquots of a single sample of normal ovarian cells obtained from a patient, pooled samples of normal ovarian cells
10 obtained from a patient, cells of a normal ovarian cell line, aliquots of a single sample of ovarian cancer cells obtained from a patient, pooled samples of ovarian cancer cells obtained from a patient, cells of an ovarian cancer cell line, or the like. In one embodiment, the samples are ovarian cancer cells obtained from a patient and a plurality of compounds known to be effective for inhibiting various ovarian cancers are tested in
15 order to identify the compound which is likely to best inhibit the ovarian cancer in the patient.

This method may likewise be used to assess the efficacy of a therapy for inhibiting ovarian cancer in a patient. In this method, the level of expression of one or more markers of the invention in a pair of samples (one subjected to the therapy, the
20 other not subjected to the therapy) is assessed. As with the method of assessing the efficacy of test compounds, if the therapy induces a significantly lower level of expression of a marker of the invention then the therapy is efficacious for inhibiting ovarian cancer. As above, if samples from a selected patient are used in this method, then alternative therapies can be assessed *in vitro* in order to select a therapy most likely
25 to be efficacious for inhibiting ovarian cancer in the patient.

As described above, the cancerous state of human ovarian cells is correlated with changes in the levels of expression of the markers of the invention. The invention includes a method for assessing the human ovarian cell carcinogenic potential of a test compound. This method comprises maintaining separate aliquots of human
30 ovarian cells in the presence and absence of the test compound. Expression of a marker of the invention in each of the aliquots is compared. A significantly higher level of expression of a marker of the invention in the aliquot maintained in the presence of the

test compound (relative to the aliquot maintained in the absence of the test compound) is an indication that the test compound possesses human ovarian cell carcinogenic potential. The relative carcinogenic potentials of various test compounds can be assessed by comparing the degree of enhancement or inhibition of the level of
5 expression of the relevant markers, by comparing the number of markers for which the level of expression is enhanced or inhibited, or by comparing both.

Various aspects of the invention are described in further detail in the following subsections.

10 I. Isolated Nucleic Acid Molecules

One aspect of the invention pertains to isolated nucleic acid molecules, including nucleic acids which encode a marker protein or a portion thereof. Isolated nucleic acids of the invention also include nucleic acid molecules sufficient for use as hybridization probes to identify marker nucleic acid molecules, and fragments of marker
15 nucleic acid molecules, *e.g.*, those suitable for use as PCR primers for the amplification or mutation of marker nucleic acid molecules. As used herein, the term "nucleic acid molecule" is intended to include DNA molecules (*e.g.*, cDNA or genomic DNA) and RNA molecules (*e.g.*, mRNA) and analogs of the DNA or RNA generated using nucleotide analogs. The nucleic acid molecule can be single-stranded or double-
20 stranded, but preferably is double-stranded DNA.

An "isolated" nucleic acid molecule is one which is separated from other nucleic acid molecules which are present in the natural source of the nucleic acid molecule. Preferably, an "isolated" nucleic acid molecule is free of sequences (preferably protein-encoding sequences) which naturally flank the nucleic acid (*i.e.*,
25 sequences located at the 5' and 3' ends of the nucleic acid) in the genomic DNA of the organism from which the nucleic acid is derived. For example, in various embodiments, the isolated nucleic acid molecule can contain less than about 5 kB, 4 kB, 3 kB, 2 kB, 1 kB, 0.5 kB or 0.1 kB of nucleotide sequences which naturally flank the nucleic acid molecule in genomic DNA of the cell from which the nucleic acid is derived. Moreover,
30 an "isolated" nucleic acid molecule, such as a cDNA molecule, can be substantially free of other cellular material, or culture medium when produced by recombinant techniques,

or substantially free of chemical precursors or other chemicals when chemically synthesized.

A nucleic acid molecule of the present invention can be isolated using standard molecular biology techniques and the sequence information in the database records described herein. Using all or a portion of such nucleic acid sequences, nucleic acid molecules of the invention can be isolated using standard hybridization and cloning techniques (*e.g.*, as described in Sambrook *et al.*, ed., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989).

A nucleic acid molecule of the invention can be amplified using cDNA, mRNA, or genomic DNA as a template and appropriate oligonucleotide primers according to standard PCR amplification techniques. The nucleic acid so amplified can be cloned into an appropriate vector and characterized by DNA sequence analysis. Furthermore, nucleotides corresponding to all or a portion of a nucleic acid molecule of the invention can be prepared by standard synthetic techniques, *e.g.*, using an automated DNA synthesizer.

In another preferred embodiment, an isolated nucleic acid molecule of the invention comprises a nucleic acid molecule which has a nucleotide sequence complementary to the nucleotide sequence of a marker nucleic acid or to the nucleotide sequence of a nucleic acid encoding a marker protein. A nucleic acid molecule which is complementary to a given nucleotide sequence is one which is sufficiently complementary to the given nucleotide sequence that it can hybridize to the given nucleotide sequence thereby forming a stable duplex.

Moreover, a nucleic acid molecule of the invention can comprise only a portion of a nucleic acid sequence, wherein the full length nucleic acid sequence comprises a marker nucleic acid or which encodes a marker protein. Such nucleic acids can be used, for example, as a probe or primer. The probe/primer typically is used as one or more substantially purified oligonucleotides. The oligonucleotide typically comprises a region of nucleotide sequence that hybridizes under stringent conditions to at least about 7, preferably about 15, more preferably about 25, 50, 75, 100, 125, 150, 175, 200, 250, 300, 350, or 400 or more consecutive nucleotides of a nucleic acid of the invention.

Probes based on the sequence of a nucleic acid molecule of the invention can be used to detect transcripts or genomic sequences corresponding to one or more markers of the invention. The probe comprises a label group attached thereto, *e.g.*, a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes
5 can be used as part of a diagnostic test kit for identifying cells or tissues which mis-express the protein, such as by measuring levels of a nucleic acid molecule encoding the protein in a sample of cells from a subject, *e.g.*, detecting mRNA levels or determining whether a gene encoding the protein has been mutated or deleted.

The invention further encompasses nucleic acid molecules that differ, due
10 to degeneracy of the genetic code, from the nucleotide sequence of nucleic acids encoding a marker protein and thus encode the same protein.

It will be appreciated by those skilled in the art that DNA sequence polymorphisms that lead to changes in the amino acid sequence can exist within a population (*e.g.*, the human population). Such genetic polymorphisms can exist among
15 individuals within a population due to natural allelic variation. An allele is one of a group of genes which occur alternatively at a given genetic locus. In addition, it will be appreciated that DNA polymorphisms that affect RNA expression levels can also exist that may affect the overall expression level of that gene (*e.g.*, by affecting regulation or degradation).

20 As used herein, the phrase "allelic variant" refers to a nucleotide sequence which occurs at a given locus or to a polypeptide encoded by the nucleotide sequence.

As used herein, the terms "gene" and "recombinant gene" refer to nucleic acid molecules comprising an open reading frame encoding a polypeptide corresponding
25 to a marker of the invention. Such natural allelic variations can typically result in 1-5% variance in the nucleotide sequence of a given gene. Alternative alleles can be identified by sequencing the gene of interest in a number of different individuals. This can be readily carried out by using hybridization probes to identify the same genetic locus in a variety of individuals. Any and all such nucleotide variations and resulting amino acid
30 polymorphisms or variations that are the result of natural allelic variation and that do not alter the functional activity are intended to be within the scope of the invention.

In another embodiment, an isolated nucleic acid molecule of the invention is at least 7, 15, 20, 25, 30, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 550, 650, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 2400, 2600, 2800, 3000, 3500, 4000, 4500, or more nucleotides in length and hybridizes under stringent
5 conditions to a marker nucleic acid or to a nucleic acid encoding a marker protein. As used herein, the term "hybridizes under stringent conditions" is intended to describe conditions for hybridization and washing under which nucleotide sequences at least 60% (65%, 70%, preferably 75%) identical to each other typically remain hybridized to each other. Such stringent conditions are known to those skilled in the art and can be found
10 in sections 6.3.1-6.3.6 of *Current Protocols in Molecular Biology*, John Wiley & Sons, N.Y. (1989). A preferred, non-limiting example of stringent hybridization conditions are hybridization in 6X sodium chloride/sodium citrate (SSC) at about 45°C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65°C.

In addition to naturally-occurring allelic variants of a nucleic acid
15 molecule of the invention that can exist in the population, the skilled artisan will further appreciate that sequence changes can be introduced by mutation thereby leading to changes in the amino acid sequence of the encoded protein, without altering the biological activity of the protein encoded thereby. For example, one can make nucleotide substitutions leading to amino acid substitutions at "non-essential" amino
20 acid residues. A "non-essential" amino acid residue is a residue that can be altered from the wild-type sequence without altering the biological activity, whereas an "essential" amino acid residue is required for biological activity. For example, amino acid residues that are not conserved or only semi-conserved among homologs of various species may be non-essential for activity and thus would be likely targets for alteration.

25 Alternatively, amino acid residues that are conserved among the homologs of various species (*e.g.*, murine and human) may be essential for activity and thus would not be likely targets for alteration.

Accordingly, another aspect of the invention pertains to nucleic acid molecules encoding a variant marker protein that contain changes in amino acid residues
30 that are not essential for activity. Such variant marker proteins differ in amino acid sequence from the naturally-occurring marker proteins, yet retain biological activity. In one embodiment, such a variant marker protein has an amino acid sequence that is at

least about 40% identical, 50%, 60%, 70%, 80%, 90%, 95%, or 98% identical to the amino acid sequence of a marker protein.

An isolated nucleic acid molecule encoding a variant marker protein can be created by introducing one or more nucleotide substitutions, additions or deletions
5 into the nucleotide sequence of marker nucleic acids, such that one or more amino acid residue substitutions, additions, or deletions are introduced into the encoded protein. Mutations can be introduced by standard techniques, such as site-directed mutagenesis and PCR-mediated mutagenesis. Preferably, conservative amino acid substitutions are made at one or more predicted non-essential amino acid residues. A "conservative
10 amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art. These families include amino acids with basic side chains (*e.g.*, lysine, arginine, histidine), acidic side chains (*e.g.*, aspartic acid, glutamic acid), uncharged polar side chains (*e.g.*, glycine, asparagine, glutamine,
15 serine, threonine, tyrosine, cysteine), non-polar side chains (*e.g.*, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (*e.g.*, threonine, valine, isoleucine) and aromatic side chains (*e.g.*, tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis,
20 and the resultant mutants can be screened for biological activity to identify mutants that retain activity. Following mutagenesis, the encoded protein can be expressed recombinantly and the activity of the protein can be determined.

The present invention encompasses antisense nucleic acid molecules, *i.e.*, molecules which are complementary to a sense nucleic acid of the invention, *e.g.*,
25 complementary to the coding strand of a double-stranded marker cDNA molecule or complementary to a marker mRNA sequence. Accordingly, an antisense nucleic acid of the invention can hydrogen bond to (*i.e.* anneal with) a sense nucleic acid of the invention. The antisense nucleic acid can be complementary to an entire coding strand, or to only a portion thereof, *e.g.*, all or part of the protein coding region (or open reading
30 frame). An antisense nucleic acid molecule can also be antisense to all or part of a non-coding region of the coding strand of a nucleotide sequence encoding a marker protein.

The non-coding regions ("5' and 3' untranslated regions") are the 5' and 3' sequences which flank the coding region and are not translated into amino acids.

An antisense oligonucleotide can be, for example, about 5, 10, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides in length. An antisense nucleic acid of the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Examples of modified nucleotides which can be used to generate the antisense nucleic acid include 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine. Alternatively, the antisense nucleic acid can be produced biologically using an expression vector into which a nucleic acid has been sub-cloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid will be of an antisense orientation to a target nucleic acid of interest, described further in the following subsection).

The antisense nucleic acid molecules of the invention are typically administered to a subject or generated *in situ* such that they hybridize with or bind to cellular mRNA and/or genomic DNA encoding a marker protein to thereby inhibit expression of the marker, *e.g.*, by inhibiting transcription and/or translation. The

hybridization can be by conventional nucleotide complementarity to form a stable duplex, or, for example, in the case of an antisense nucleic acid molecule which binds to DNA duplexes, through specific interactions in the major groove of the double helix. Examples of a route of administration of antisense nucleic acid molecules of the invention includes direct injection at a tissue site or infusion of the antisense nucleic acid into an ovary-associated body fluid. Alternatively, antisense nucleic acid molecules can be modified to target selected cells and then administered systemically. For example, for systemic administration, antisense molecules can be modified such that they specifically bind to receptors or antigens expressed on a selected cell surface, *e.g.*, by linking the antisense nucleic acid molecules to peptides or antibodies which bind to cell surface receptors or antigens. The antisense nucleic acid molecules can also be delivered to cells using the vectors described herein. To achieve sufficient intracellular concentrations of the antisense molecules, vector constructs in which the antisense nucleic acid molecule is placed under the control of a strong pol II or pol III promoter are preferred.

An antisense nucleic acid molecule of the invention can be an α -anomeric nucleic acid molecule. An α -anomeric nucleic acid molecule forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual α -units, the strands run parallel to each other (Gaultier *et al.*, 1987, *Nucleic Acids Res.* 15:6625-6641). The antisense nucleic acid molecule can also comprise a 2'-O-methylribonucleotide (Inoue *et al.*, 1987, *Nucleic Acids Res.* 15:6131-6148) or a chimeric RNA-DNA analogue (Inoue *et al.*, 1987, *FEBS Lett.* 215:327-330).

The invention also encompasses ribozymes. Ribozymes are catalytic RNA molecules with ribonuclease activity which are capable of cleaving a single-stranded nucleic acid, such as an mRNA, to which they have a complementary region. Thus, ribozymes (*e.g.*, hammerhead ribozymes as described in Haselhoff and Gerlach, 1988, *Nature* 334:585-591) can be used to catalytically cleave mRNA transcripts to thereby inhibit translation of the protein encoded by the mRNA. A ribozyme having specificity for a nucleic acid molecule encoding a marker protein can be designed based upon the nucleotide sequence of a cDNA corresponding to the marker. For example, a derivative of a *Tetrahymena* L-19 IVS RNA can be constructed in which the nucleotide sequence of the active site is complementary to the nucleotide sequence to be cleaved

(see Cech *et al.* U.S. Patent No. 4,987,071; and Cech *et al.* U.S. Patent No. 5,116,742). Alternatively, an mRNA encoding a polypeptide of the invention can be used to select a catalytic RNA having a specific ribonuclease activity from a pool of RNA molecules (see, *e.g.*, Bartel and Szostak, 1993, *Science* 261:1411-1418).

5 The invention also encompasses nucleic acid molecules which form triple helical structures. For example, expression of a marker of the invention can be inhibited by targeting nucleotide sequences complementary to the regulatory region of the gene encoding the marker nucleic acid or protein (*e.g.*, the promoter and/or enhancer) to form triple helical structures that prevent transcription of the gene in target cells. See
10 generally Helene (1991) *Anticancer Drug Des.* 6(6):569-84; Helene (1992) *Ann. N.Y. Acad. Sci.* 660:27-36; and Maher (1992) *Bioassays* 14(12):807-15.

 In various embodiments, the nucleic acid molecules of the invention can be modified at the base moiety, sugar moiety or phosphate backbone to improve, *e.g.*, the stability, hybridization, or solubility of the molecule. For example, the deoxyribose
15 phosphate backbone of the nucleic acids can be modified to generate peptide nucleic acids (see Hyrup *et al.*, 1996, *Bioorganic & Medicinal Chemistry* 4(1): 5-23). As used herein, the terms "peptide nucleic acids" or "PNAs" refer to nucleic acid mimics, *e.g.*, DNA mimics, in which the deoxyribose phosphate backbone is replaced by a pseudopeptide backbone and only the four natural nucleobases are retained. The neutral
20 backbone of PNAs has been shown to allow for specific hybridization to DNA and RNA under conditions of low ionic strength. The synthesis of PNA oligomers can be performed using standard solid phase peptide synthesis protocols as described in Hyrup *et al.* (1996), *supra*; Perry-O'Keefe *et al.* (1996) *Proc. Natl. Acad. Sci. USA* 93:14670-675.

25 PNAs can be used in therapeutic and diagnostic applications. For example, PNAs can be used as antisense or antigene agents for sequence-specific modulation of gene expression by, *e.g.*, inducing transcription or translation arrest or inhibiting replication. PNAs can also be used, *e.g.*, in the analysis of single base pair mutations in a gene by, *e.g.*, PNA directed PCR clamping; as artificial restriction
30 enzymes when used in combination with other enzymes, *e.g.*, S1 nucleases (Hyrup (1996), *supra*; or as probes or primers for DNA sequence and hybridization (Hyrup, 1996, *supra*; Perry-O'Keefe *et al.*, 1996, *Proc. Natl. Acad. Sci. USA* 93:14670-675).

In another embodiment, PNAs can be modified, *e.g.*, to enhance their stability or cellular uptake, by attaching lipophilic or other helper groups to PNA, by the formation of PNA-DNA chimeras, or by the use of liposomes or other techniques of drug delivery known in the art. For example, PNA-DNA chimeras can be generated
5 which can combine the advantageous properties of PNA and DNA. Such chimeras allow DNA recognition enzymes, *e.g.*, RNase H and DNA polymerases, to interact with the DNA portion while the PNA portion would provide high binding affinity and specificity. PNA-DNA chimeras can be linked using linkers of appropriate lengths selected in terms of base stacking, number of bonds between the nucleobases, and
10 orientation (Hyrup, 1996, *supra*). The synthesis of PNA-DNA chimeras can be performed as described in Hyrup (1996), *supra*, and Finn *et al.* (1996) *Nucleic Acids Res.* 24(17):3357-63. For example, a DNA chain can be synthesized on a solid support using standard phosphoramidite coupling chemistry and modified nucleoside analogs. Compounds such as 5'-(4-methoxytrityl)amino-5'-deoxy-thymidine phosphoramidite can
15 be used as a link between the PNA and the 5' end of DNA (Mag *et al.*, 1989, *Nucleic Acids Res.* 17:5973-88). PNA monomers are then coupled in a step-wise manner to produce a chimeric molecule with a 5' PNA segment and a 3' DNA segment (Finn *et al.*, 1996, *Nucleic Acids Res.* 24(17):3357-63). Alternatively, chimeric molecules can be synthesized with a 5' DNA segment and a 3' PNA segment (Peterser *et al.*, 1975,
20 *Bioorganic Med. Chem. Lett.* 5:1119-11124).

In other embodiments, the oligonucleotide can include other appended groups such as peptides (*e.g.*, for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:6553-6556; Lemaitre *et al.*, 1987, *Proc. Natl. Acad. Sci. USA*
25 84:648-652; PCT Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT Publication No. WO 89/10134). In addition, oligonucleotides can be modified with hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, 1988, *Bio/Techniques* 6:958-976) or intercalating agents (see, *e.g.*, Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide can be conjugated to another molecule, *e.g.*, a peptide,
30 hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The invention also includes molecular beacon nucleic acids having at least one region which is complementary to a nucleic acid of the invention, such that the molecular beacon is useful for quantitating the presence of the nucleic acid of the invention in a sample. A "molecular beacon" nucleic acid is a nucleic acid comprising a pair of complementary regions and having a fluorophore and a fluorescent quencher associated therewith. The fluorophore and quencher are associated with different portions of the nucleic acid in such an orientation that when the complementary regions are annealed with one another, fluorescence of the fluorophore is quenched by the quencher. When the complementary regions of the nucleic acid are not annealed with one another, fluorescence of the fluorophore is quenched to a lesser degree. Molecular beacon nucleic acids are described, for example, in U.S. Patent 5,876,930.

II. Isolated Proteins and Antibodies

One aspect of the invention pertains to isolated marker proteins and biologically active portions thereof, as well as polypeptide fragments suitable for use as immunogens to raise antibodies directed against a marker protein or a fragment thereof. In one embodiment, the native marker protein can be isolated from cells or tissue sources by an appropriate purification scheme using standard protein purification techniques. In another embodiment, a protein or peptide comprising the whole or a segment of the marker protein is produced by recombinant DNA techniques. Alternative to recombinant expression, such protein or peptide can be synthesized chemically using standard peptide synthesis techniques.

An "isolated" or "purified" protein or biologically active portion thereof is substantially free of cellular material or other contaminating proteins from the cell or tissue source from which the protein is derived, or substantially free of chemical precursors or other chemicals when chemically synthesized. The language "substantially free of cellular material" includes preparations of protein in which the protein is separated from cellular components of the cells from which it is isolated or recombinantly produced. Thus, protein that is substantially free of cellular material includes preparations of protein having less than about 30%, 20%, 10%, or 5% (by dry weight) of heterologous protein (also referred to herein as a "contaminating protein"). When the protein or biologically active portion thereof is recombinantly produced, it is

also preferably substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, 10%, or 5% of the volume of the protein preparation. When the protein is produced by chemical synthesis, it is preferably substantially free of chemical precursors or other chemicals, *i.e.*, it is separated from chemical precursors or other chemicals which are involved in the synthesis of the protein. Accordingly such preparations of the protein have less than about 30%, 20%, 10%, 5% (by dry weight) of chemical precursors or compounds other than the polypeptide of interest.

Biologically active portions of a marker protein include polypeptides comprising amino acid sequences sufficiently identical to or derived from the amino acid sequence of the marker protein, which include fewer amino acids than the full length protein, and exhibit at least one activity of the corresponding full-length protein. Typically, biologically active portions comprise a domain or motif with at least one activity of the corresponding full-length protein. A biologically active portion of a marker protein of the invention can be a polypeptide which is, for example, 10, 25, 50, 100 or more amino acids in length. Moreover, other biologically active portions, in which other regions of the marker protein are deleted, can be prepared by recombinant techniques and evaluated for one or more of the functional activities of the native form of the marker protein.

Preferred marker proteins are encoded by nucleotide sequences comprising the sequences listed in Tables 1-3. Other useful proteins are substantially identical (*e.g.*, at least about 40%, preferably 50%, 60%, 70%, 80%, 90%, 95%, or 99%) to one of these sequences and retain the functional activity of the corresponding naturally-occurring marker protein yet differ in amino acid sequence due to natural allelic variation or mutagenesis.

To determine the percent identity of two amino acid sequences or of two nucleic acids, the sequences are aligned for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first amino acid or nucleic acid sequence for optimal alignment with a second amino or nucleic acid sequence). The amino acid residues or nucleotides at corresponding amino acid positions or nucleotide positions are then compared. When a position in the first sequence is occupied by the same amino acid residue or nucleotide as the corresponding position in the second sequence, then the molecules are identical at that position. The percent identity between the two sequences

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is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions (*e.g.*, overlapping positions) $\times 100$). In one embodiment the two sequences are the same length.

The determination of percent identity between two sequences can be accomplished using a mathematical algorithm. A preferred, non-limiting example of a mathematical algorithm utilized for the comparison of two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264-2268, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the BLASTN and BLASTX programs of Altschul, *et al.* (1990) *J. Mol. Biol.* 215:403-410. BLAST nucleotide searches can be performed with the BLASTN program, score = 100, wordlength = 12 to obtain nucleotide sequences homologous to a nucleic acid molecules of the invention. BLAST protein searches can be performed with the BLASTP program, score = 50, wordlength = 3 to obtain amino acid sequences homologous to a protein molecules of the invention. To obtain gapped alignments for comparison purposes, a newer version of the BLAST algorithm called Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389-3402, which is able to perform gapped local alignments for the programs BLASTN, BLASTP and BLASTX. Alternatively, PSI-Blast can be used to perform an iterated search which detects distant relationships between molecules. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (*e.g.*, BLASTX and BLASTN) can be used. Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, (1988) *CABIOS* 4:11-17. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Yet another useful algorithm for identifying regions of local sequence similarity and alignment is the FASTA algorithm as described in Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85:2444-2448. When using the FASTA algorithm for comparing nucleotide or amino acid sequences, a PAM120 weight residue table can, for example, be used with a *k*-tuple value of 2.

The percent identity between two sequences can be determined using techniques similar to those described above, with or without allowing gaps. In calculating percent identity, only exact matches are counted.

The invention also provides chimeric or fusion proteins comprising a marker protein or a segment thereof. As used herein, a "chimeric protein" or "fusion protein" comprises all or part (preferably a biologically active part) of a marker protein operably linked to a heterologous polypeptide (*i.e.*, a polypeptide other than the marker protein). Within the fusion protein, the term "operably linked" is intended to indicate that the marker protein or segment thereof and the heterologous polypeptide are fused in-frame to each other. The heterologous polypeptide can be fused to the amino-terminus or the carboxyl-terminus of the marker protein or segment.

One useful fusion protein is a GST fusion protein in which a marker protein or segment is fused to the carboxyl terminus of GST sequences. Such fusion proteins can facilitate the purification of a recombinant polypeptide of the invention.

In another embodiment, the fusion protein contains a heterologous signal sequence at its amino terminus. For example, the native signal sequence of a marker protein can be removed and replaced with a signal sequence from another protein. For example, the gp67 secretory sequence of the baculovirus envelope protein can be used as a heterologous signal sequence (Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, 1992). Other examples of eukaryotic heterologous signal sequences include the secretory sequences of melittin and human placental alkaline phosphatase (Stratagene; La Jolla, California). In yet another example, useful prokaryotic heterologous signal sequences include the phoA secretory signal (Sambrook *et al.*, *supra*) and the protein A secretory signal (Pharmacia Biotech; Piscataway, New Jersey).

In yet another embodiment, the fusion protein is an immunoglobulin fusion protein in which all or part of a marker protein is fused to sequences derived from a member of the immunoglobulin protein family. The immunoglobulin fusion proteins of the invention can be incorporated into pharmaceutical compositions and administered to a subject to inhibit an interaction between a ligand (soluble or membrane-bound) and a protein on the surface of a cell (receptor), to thereby suppress signal transduction *in vivo*. The immunoglobulin fusion protein can be used to affect the bioavailability of a

cognate ligand of a marker protein. Inhibition of ligand/receptor interaction can be useful therapeutically, both for treating proliferative and differentiative disorders and for modulating (*e.g.* promoting or inhibiting) cell survival. Moreover, the immunoglobulin fusion proteins of the invention can be used as immunogens to produce antibodies
5 directed against a marker protein in a subject, to purify ligands and in screening assays to identify molecules which inhibit the interaction of the marker protein with ligands.

Chimeric and fusion proteins of the invention can be produced by standard recombinant DNA techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers.
10 Alternatively, PCR amplification of gene fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive gene fragments which can subsequently be annealed and re-amplified to generate a chimeric gene sequence (see, *e.g.*, Ausubel *et al.*, *supra*). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST polypeptide).
15 A nucleic acid encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide of the invention.

A signal sequence can be used to facilitate secretion and isolation of marker proteins. Signal sequences are typically characterized by a core of hydrophobic
20 amino acids which are generally cleaved from the mature protein during secretion in one or more cleavage events. Such signal peptides contain processing sites that allow cleavage of the signal sequence from the mature proteins as they pass through the secretory pathway. Thus, the invention pertains to marker proteins, fusion proteins or segments thereof having a signal sequence, as well as to such proteins from which the
25 signal sequence has been proteolytically cleaved (*i.e.*, the cleavage products). In one embodiment, a nucleic acid sequence encoding a signal sequence can be operably linked in an expression vector to a protein of interest, such as a marker protein or a segment thereof. The signal sequence directs secretion of the protein, such as from a eukaryotic host into which the expression vector is transformed, and the signal sequence is
30 subsequently or concurrently cleaved. The protein can then be readily purified from the extracellular medium by art recognized methods. Alternatively, the signal sequence can

be linked to the protein of interest using a sequence which facilitates purification, such as with a GST domain.

The present invention also pertains to variants of the marker proteins. Such variants have an altered amino acid sequence which can function as either agonists (mimetics) or as antagonists. Variants can be generated by mutagenesis, *e.g.*, discrete point mutation or truncation. An agonist can retain substantially the same, or a subset, of the biological activities of the naturally occurring form of the protein. An antagonist of a protein can inhibit one or more of the activities of the naturally occurring form of the protein by, for example, competitively binding to a downstream or upstream member of a cellular signaling cascade which includes the protein of interest. Thus, specific biological effects can be elicited by treatment with a variant of limited function. Treatment of a subject with a variant having a subset of the biological activities of the naturally occurring form of the protein can have fewer side effects in a subject relative to treatment with the naturally occurring form of the protein.

Variants of a marker protein which function as either agonists (mimetics) or as antagonists can be identified by screening combinatorial libraries of mutants, *e.g.*, truncation mutants, of the protein of the invention for agonist or antagonist activity. In one embodiment, a variegated library of variants is generated by combinatorial mutagenesis at the nucleic acid level and is encoded by a variegated gene library. A variegated library of variants can be produced by, for example, enzymatically ligating a mixture of synthetic oligonucleotides into gene sequences such that a degenerate set of potential protein sequences is expressible as individual polypeptides, or alternatively, as a set of larger fusion proteins (*e.g.*, for phage display). There are a variety of methods which can be used to produce libraries of potential variants of the marker proteins from a degenerate oligonucleotide sequence. Methods for synthesizing degenerate oligonucleotides are known in the art (see, *e.g.*, Narang, 1983, *Tetrahedron* 39:3; Itakura *et al.*, 1984, *Annu. Rev. Biochem.* 53:323; Itakura *et al.*, 1984, *Science* 198:1056; Ike *et al.*, 1983 *Nucleic Acid Res.* 11:477).

In addition, libraries of segments of a marker protein can be used to generate a variegated population of polypeptides for screening and subsequent selection of variant marker proteins or segments thereof. For example, a library of coding sequence fragments can be generated by treating a double stranded PCR fragment of the

coding sequence of interest with a nuclease under conditions wherein nicking occurs only about once per molecule, denaturing the double stranded DNA, renaturing the DNA to form double stranded DNA which can include sense/antisense pairs from different nicked products, removing single stranded portions from reformed duplexes by
5 treatment with S1 nuclease, and ligating the resulting fragment library into an expression vector. By this method, an expression library can be derived which encodes amino terminal and internal fragments of various sizes of the protein of interest.

Several techniques are known in the art for screening gene products of combinatorial libraries made by point mutations or truncation, and for screening cDNA
10 libraries for gene products having a selected property. The most widely used techniques, which are amenable to high through-put analysis, for screening large gene libraries typically include cloning the gene library into replicable expression vectors, transforming appropriate cells with the resulting library of vectors, and expressing the combinatorial genes under conditions in which detection of a desired activity facilitates
15 isolation of the vector encoding the gene whose product was detected. Recursive ensemble mutagenesis (REM), a technique which enhances the frequency of functional mutants in the libraries, can be used in combination with the screening assays to identify variants of a protein of the invention (Arkin and Yourvan, 1992, *Proc. Natl. Acad. Sci. USA* 89:7811-7815; Delgrave *et al.*, 1993, *Protein Engineering* 6(3):327- 331).

20 Another aspect of the invention pertains to antibodies directed against a protein of the invention. In preferred embodiments, the antibodies specifically bind a marker protein or a fragment thereof. The terms "antibody" and "antibodies" as used interchangeably herein refer to immunoglobulin molecules as well as fragments and derivatives thereof that comprise an immunologically active portion of an
25 immunoglobulin molecule, (*i.e.*, such a portion contains an antigen binding site which specifically binds an antigen, such as a marker protein, *e.g.*, an epitope of a marker protein). An antibody which specifically binds to a protein of the invention is an antibody which binds the protein, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the protein. Examples of an
30 immunologically active portion of an immunoglobulin molecule include, but are not limited to, single-chain antibodies (scAb), F(ab) and F(ab')₂ fragments.

An isolated protein of the invention or a fragment thereof can be used as an immunogen to generate antibodies. The full-length protein can be used or, alternatively, the invention provides antigenic peptide fragments for use as immunogens. The antigenic peptide of a protein of the invention comprises at least 8 (preferably 10,
5 15, 20, or 30 or more) amino acid residues of the amino acid sequence of one of the proteins of the invention, and encompasses at least one epitope of the protein such that an antibody raised against the peptide forms a specific immune complex with the protein. Preferred epitopes encompassed by the antigenic peptide are regions that are located on the surface of the protein, *e.g.*, hydrophilic regions. Hydrophobicity
10 sequence analysis, hydrophilicity sequence analysis, or similar analyses can be used to identify hydrophilic regions. In preferred embodiments, an isolated marker protein or fragment thereof is used as an immunogen.

An immunogen typically is used to prepare antibodies by immunizing a suitable (*i.e.* immunocompetent) subject such as a rabbit, goat, mouse, or other mammal
15 or vertebrate. An appropriate immunogenic preparation can contain, for example, recombinantly-expressed or chemically-synthesized protein or peptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or a similar immunostimulatory agent. Preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made
20 using a non-human host cell for recombinant expression of a protein of the invention. In such a manner, the resulting antibody compositions have reduced or no binding of human proteins other than a protein of the invention.

The invention provides polyclonal and monoclonal antibodies. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to
25 a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope. Preferred polyclonal and monoclonal antibody compositions are ones that have been selected for antibodies directed against a protein of the invention. Particularly preferred polyclonal and monoclonal antibody preparations are ones that contain only antibodies directed against
30 a marker protein or fragment thereof.

Polyclonal antibodies can be prepared by immunizing a suitable subject with a protein of the invention as an immunogen. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. At an appropriate time after immunization, *e.g.*, when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies (mAb) by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell hybridoma technique (see Kozbor *et al.*, 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (see Cole *et al.*, pp. 77-96 In *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., 1985) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology*, Coligan *et al.* ed., John Wiley & Sons, New York, 1994). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, *e.g.*, using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a protein of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.* (1991) *Bio/Technology* 9:1370-1372; Hay *et al.* (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse *et al.* (1989) *Science* 246:1275-1281; Griffiths *et al.* (1993) *EMBO J.* 12:725-734.

The invention also provides recombinant antibodies that specifically bind a protein of the invention. In preferred embodiments, the recombinant antibodies specifically binds a marker protein or fragment thereof. Recombinant antibodies include, but are not limited to, chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, single-chain antibodies and multi-specific antibodies. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, *e.g.*, Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Single-chain antibodies have an antigen binding site and consist of single polypeptides. They can be produced by techniques known in the art, for example using methods described in Ladner *et al.* U.S. Pat. No. 4,946,778 (which is incorporated herein by reference in its entirety); Bird *et al.*, (1988) *Science* 242:423-426; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:1-9; Whitlow *et al.*, (1991) *Methods in Enzymology* 2:97-105; and Huston *et al.*, (1991) *Methods in Enzymology Molecular Design and Modeling: Concepts and Applications* 203:46-88. Multi-specific antibodies are antibody molecules having at least two antigen-binding sites that specifically bind different antigens. Such molecules can be produced by techniques known in the art, for example using methods described in Segal, U.S. Patent No. 4,676,980 (the disclosure of which is incorporated herein by reference in its entirety); Holliger et al., (1993) *Proc. Natl. Acad. Sci. USA* 90:6444-6448; Whitlow *et al.*, (1994) *Protein Eng.* 7:1017-1026 and U.S. Pat. No. 6,121,424.

Humanized antibodies are antibody molecules from non-human species having one or more complementarity determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, *e.g.*, Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better *et al.* (1988) *Science* 240:1041-1043; Liu *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu

et al. (1987) *J. Immunol.* 139:3521- 3526; Sun *et al.* (1987) *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura *et al.* (1987) *Cancer Res.* 47:999-1005; Wood *et al.* (1985) *Nature* 314:446-449; and Shaw *et al.* (1988) *J. Natl. Cancer Inst.* 80:1553-1559); Morrison (1985) *Science* 229:1202-1207; Oi *et al.* (1986) *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones *et al.* (1986) *Nature* 321:552-525; Verhoeyan *et al.* (1988) *Science* 239:1534; and Beidler *et al.* (1988) *J. Immunol.* 141:4053-4060.

More particularly, humanized antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, *e.g.*, all or a portion of a polypeptide corresponding to a marker of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar (1995) *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, *e.g.*, U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, *e.g.*, a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope (Jespers *et al.*, 1994, *Bio/technology* 12:899-903).

The antibodies of the invention can be isolated after production (*e.g.*, from the blood or serum of the subject) or synthesis and further purified by well-known techniques. For example, IgG antibodies can be purified using protein A chromatography. Antibodies specific for a protein of the invention can be selected or

(*e.g.*, partially purified) or purified by, *e.g.*, affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, *i.e.*, one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those of the desired protein of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein of the invention.

In a preferred embodiment, the substantially purified antibodies of the invention may specifically bind to a signal peptide, a secreted sequence, an extracellular domain, a transmembrane or a cytoplasmic domain or cytoplasmic membrane of a protein of the invention. In a particularly preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a protein of the invention. In a more preferred embodiment, the substantially purified antibodies of the invention specifically bind to a secreted sequence or an extracellular domain of the amino acid sequences of a marker protein.

An antibody directed against a protein of the invention can be used to isolate the protein by standard techniques, such as affinity chromatography or immunoprecipitation. Moreover, such an antibody can be used to detect the marker protein or fragment thereof (*e.g.*, in a cellular lysate or cell supernatant) in order to evaluate the level and pattern of expression of the marker. The antibodies can also be used diagnostically to monitor protein levels in tissues or body fluids (*e.g.* in an ovary-associated body fluid) as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by the

use of an antibody derivative, which comprises an antibody of the invention coupled to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish
5 peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol;
10 examples of bioluminescent materials include luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{35}S or ^3H .

Antibodies of the invention may also be used as therapeutic agents in treating cancers. In a preferred embodiment, completely human antibodies of the invention are used for therapeutic treatment of human cancer patients, particularly those
15 having an ovarian cancer. In another preferred embodiment, antibodies that bind specifically to a marker protein or fragment thereof are used for therapeutic treatment. Further, such therapeutic antibody may be an antibody derivative or immunotoxin comprising an antibody conjugated to a therapeutic moiety such as a cytotoxin, a therapeutic agent or a radioactive metal ion. A cytotoxin or cytotoxic agent includes any
20 agent that is detrimental to cells. Examples include taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof.
25 Therapeutic agents include, but are not limited to, antimetabolites (*e.g.*, methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.*, mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines
30 (*e.g.*, daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.*, dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (*e.g.*, vincristine and vinblastine).

The conjugated antibodies of the invention can be used for modifying a given biological response, for the drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as ribosome-inhibiting protein (see Better et al., U.S. Patent No. 6,146,631, the disclosure of which is incorporated herein in its entirety), abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, .alpha.-interferon, .beta.-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, *e.g.*, Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.*, 62:119-58 (1982).

Accordingly, in one aspect, the invention provides substantially purified antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. In various embodiments, the substantially purified antibodies of the invention, or fragments or derivatives thereof, can be human, non-human, chimeric and/or humanized antibodies. In another aspect, the invention provides non-human antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. Such non-human antibodies can be goat, mouse, sheep, horse, chicken, rabbit, or rat

antibodies. Alternatively, the non-human antibodies of the invention can be chimeric and/or humanized antibodies. In addition, the non-human antibodies of the invention can be polyclonal antibodies or monoclonal antibodies. In still a further aspect, the invention provides monoclonal antibodies, antibody fragments and derivatives, all of which specifically bind to a protein of the invention and preferably, a marker protein. The monoclonal antibodies can be human, humanized, chimeric and/or non-human antibodies.

The invention also provides a kit containing an antibody of the invention conjugated to a detectable substance, and instructions for use. Still another aspect of the invention is a pharmaceutical composition comprising an antibody of the invention and a pharmaceutically acceptable carrier. In preferred embodiments, the pharmaceutical composition contains an antibody of the invention, a therapeutic moiety, and a pharmaceutically acceptable carrier.

15 III. Recombinant Expression Vectors and Host Cells

Another aspect of the invention pertains to vectors, preferably expression vectors, containing a nucleic acid encoding a marker protein (or a portion of such a protein). As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, namely expression vectors, are capable of directing the expression of genes to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids (vectors). However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective

retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The recombinant expression vectors of the invention comprise a nucleic acid of the invention in a form suitable for expression of the nucleic acid in a host cell.

5 This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" is intended to mean that the nucleotide sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression
10 of the nucleotide sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, *Methods in Enzymology: Gene Expression Technology* vol.185,
15 Academic Press, San Diego, CA (1991). Regulatory sequences include those which direct constitutive expression of a nucleotide sequence in many types of host cell and those which direct expression of the nucleotide sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the
20 host cell to be transformed, the level of expression of protein desired, and the like. The expression vectors of the invention can be introduced into host cells to thereby produce proteins or peptides, including fusion proteins or peptides, encoded by nucleic acids as described herein.

The recombinant expression vectors of the invention can be designed for
25 expression of a marker protein or a segment thereof in prokaryotic (*e.g.*, *E. coli*) or eukaryotic cells (*e.g.*, insect cells {using baculovirus expression vectors}, yeast cells or mammalian cells). Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

30 Expression of proteins in prokaryotes is most often carried out in *E. coli* with vectors containing constitutive or inducible promoters directing the expression of either fusion or non-fusion proteins. Fusion vectors add a number of amino acids to a

protein encoded therein, usually to the amino terminus of the recombinant protein. Such fusion vectors typically serve three purposes: 1) to increase expression of recombinant protein; 2) to increase the solubility of the recombinant protein; and 3) to aid in the purification of the recombinant protein by acting as a ligand in affinity purification.

- 5 Often, in fusion expression vectors, a proteolytic cleavage site is introduced at the junction of the fusion moiety and the recombinant protein to enable separation of the recombinant protein from the fusion moiety subsequent to purification of the fusion protein. Such enzymes, and their cognate recognition sequences, include Factor Xa, thrombin and enterokinase. Typical fusion expression vectors include pGEX
- 10 (Pharmacia Biotech Inc; Smith and Johnson, 1988, *Gene* 67:31-40), pMAL (New England Biolabs, Beverly, MA) and pRIT5 (Pharmacia, Piscataway, NJ) which fuse glutathione S-transferase (GST), maltose E binding protein, or protein A, respectively, to the target recombinant protein.

- Examples of suitable inducible non-fusion *E. coli* expression vectors
- 15 include pTrc (Amann *et al.*, 1988, *Gene* 69:301-315) and pET 11d (Studier *et al.*, p. 60-89, In *Gene Expression Technology: Methods in Enzymology* vol.185, Academic Press, San Diego, CA, 1991). Target gene expression from the pTrc vector relies on host RNA polymerase transcription from a hybrid trp-lac fusion promoter. Target gene expression from the pET 11d vector relies on transcription from a T7 gn10-lac fusion promoter
- 20 mediated by a co-expressed viral RNA polymerase (T7 gn1). This viral polymerase is supplied by host strains BL21(DE3) or HMS174(DE3) from a resident prophage harboring a T7 gn1 gene under the transcriptional control of the lacUV 5 promoter.

- One strategy to maximize recombinant protein expression in *E. coli* is to express the protein in a host bacteria with an impaired capacity to proteolytically cleave
- 25 the recombinant protein (Gottesman, p. 119-128, In *Gene Expression Technology: Methods in Enzymology* vol. 185, Academic Press, San Diego, CA, 1990. Another strategy is to alter the nucleic acid sequence of the nucleic acid to be inserted into an expression vector so that the individual codons for each amino acid are those preferentially utilized in *E. coli* (Wada *et al.*, 1992, *Nucleic Acids Res.* 20:2111-2118).
- 30 Such alteration of nucleic acid sequences of the invention can be carried out by standard DNA synthesis techniques.

In another embodiment, the expression vector is a yeast expression vector. Examples of vectors for expression in yeast *S. cerevisiae* include pYepSec1 (Baldari *et al.*, 1987, *EMBO J.* 6:229-234), pMFa (Kurjan and Herskowitz, 1982, *Cell* 30:933-943), pJRY88 (Schultz *et al.*, 1987, *Gene* 54:113-123), pYES2 (Invitrogen Corporation, San Diego, CA), and pPicZ (Invitrogen Corp, San Diego, CA).

Alternatively, the expression vector is a baculovirus expression vector. Baculovirus vectors available for expression of proteins in cultured insect cells (*e.g.*, Sf 9 cells) include the pAc series (Smith *et al.*, 1983, *Mol. Cell Biol.* 3:2156-2165) and the pVL series (Lucklow and Summers, 1989, *Virology* 170:31-39).

10 In yet another embodiment, a nucleic acid of the invention is expressed in mammalian cells using a mammalian expression vector. Examples of mammalian expression vectors include pCDM8 (Seed, 1987, *Nature* 329:840) and pMT2PC (Kaufman *et al.*, 1987, *EMBO J.* 6:187-195). When used in mammalian cells, the expression vector's control functions are often provided by viral regulatory elements.

15 For example, commonly used promoters are derived from polyoma, Adenovirus 2, cytomegalovirus and Simian Virus 40. For other suitable expression systems for both prokaryotic and eukaryotic cells see chapters 16 and 17 of Sambrook *et al.*, *supra*.

In another embodiment, the recombinant mammalian expression vector is capable of directing expression of the nucleic acid preferentially in a particular cell type

20 (*e.g.*, tissue-specific regulatory elements are used to express the nucleic acid). Tissue-specific regulatory elements are known in the art. Non-limiting examples of suitable tissue-specific promoters include the albumin promoter (liver-specific; Pinkert *et al.*, 1987, *Genes Dev.* 1:268-277), lymphoid-specific promoters (Calame and Eaton, 1988, *Adv. Immunol.* 43:235-275), in particular promoters of T cell receptors (Winoto and

25 Baltimore, 1989, *EMBO J.* 8:729-733) and immunoglobulins (Banerji *et al.*, 1983, *Cell* 33:729-740; Queen and Baltimore, 1983, *Cell* 33:741-748), neuron-specific promoters (*e.g.*, the neurofilament promoter; Byrne and Ruddle, 1989, *Proc. Natl. Acad. Sci. USA* 86:5473-5477), pancreas-specific promoters (Edlund *et al.*, 1985, *Science* 230:912-916), and mammary gland-specific promoters (*e.g.*, milk whey promoter; U.S. Patent No.

30 4,873,316 and European Application Publication No. 264,166). Developmentally-regulated promoters are also encompassed, for example the murine hox promoters

(Kessel and Gruss, 1990, *Science* 249:374-379) and the α -fetoprotein promoter (Camper and Tilghman, 1989, *Genes Dev.* 3:537-546).

The invention further provides a recombinant expression vector comprising a DNA molecule of the invention cloned into the expression vector in an antisense orientation. That is, the DNA molecule is operably linked to a regulatory
5 sequence in a manner which allows for expression (by transcription of the DNA molecule) of an RNA molecule which is antisense to the mRNA encoding a polypeptide of the invention. Regulatory sequences operably linked to a nucleic acid cloned in the antisense orientation can be chosen which direct the continuous expression of the
10 antisense RNA molecule in a variety of cell types, for instance viral promoters and/or enhancers, or regulatory sequences can be chosen which direct constitutive, tissue-specific or cell type specific expression of antisense RNA. The antisense expression vector can be in the form of a recombinant plasmid, phagemid, or attenuated virus in which antisense nucleic acids are produced under the control of a high efficiency
15 regulatory region, the activity of which can be determined by the cell type into which the vector is introduced. For a discussion of the regulation of gene expression using antisense genes see Weintraub *et al.*, 1986, *Trends in Genetics*, Vol. 1(1).

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host
20 cell" and "recombinant host cell" are used interchangeably herein. It is understood that such terms refer not only to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term
25 as used herein.

A host cell can be any prokaryotic (*e.g.*, *E. coli*) or eukaryotic cell (*e.g.*, insect cells, yeast or mammalian cells).

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms
30 "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing foreign nucleic acid into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection,

lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells
5 may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced nucleic acid
10 can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic or eukaryotic host cell in culture, can be used to produce a marker protein or a segment thereof. Accordingly, the invention further provides methods for producing a marker protein or a segment
15 thereof using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of the invention (into which a recombinant expression vector encoding a marker protein or a segment thereof has been introduced) in a suitable medium such that the is produced. In another embodiment, the method further comprises isolating the a marker protein or a segment thereof from the medium or the
20 host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a sequences encoding a marker protein or a segment thereof have been introduced. Such host cells can then be used to
25 create non-human transgenic animals in which exogenous sequences encoding a marker protein of the invention have been introduced into their genome or homologous recombinant animals in which endogenous gene(s) encoding a marker protein have been altered. Such animals are useful for studying the function and/or activity of the marker protein and for identifying and/or evaluating modulators of marker protein. As used
30 herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human

primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

10 A transgenic animal of the invention can be created by introducing a nucleic acid encoding a marker protein into the male pronuclei of a fertilized oocyte, *e.g.*, by microinjection, retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. A tissue-specific regulatory sequence(s) can be operably linked to the
15 transgene to direct expression of the polypeptide of the invention to particular cells. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No.
20 4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986. Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the transgene in its genome and/or expression of mRNA encoding the transgene in tissues or cells of the animals. A transgenic founder animal
25 can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying the transgene can further be bred to other transgenic animals carrying other transgenes.

 To create an homologous recombinant animal, a vector is prepared which contains at least a portion of a gene encoding a marker protein into which a deletion,
30 addition or substitution has been introduced to thereby alter, *e.g.*, functionally disrupt, the gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous gene is functionally disrupted (*i.e.*, no longer encodes a

functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous gene is mutated or otherwise altered but still encodes functional protein (*e.g.*, the upstream regulatory region can be altered to thereby alter the expression of the endogenous protein). In the homologous recombination vector, the altered portion of the gene is flanked at its 5' and 3' ends by additional nucleic acid of the gene to allow for homologous recombination to occur between the exogenous gene carried by the vector and an endogenous gene in an embryonic stem cell. The additional flanking nucleic acid sequences are of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (see, *e.g.*, Thomas and Capecchi, 1987, *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (*e.g.*, by electroporation) and cells in which the introduced gene has homologously recombined with the endogenous gene are selected (see, *e.g.*, Li *et al.*, 1992, *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (*e.g.*, a mouse) to form aggregation chimeras (see, *e.g.*, Bradley, *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, Ed., IRL, Oxford, 1987, pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication NOS. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

In another embodiment, transgenic non-human animals can be produced which contain selected systems which allow for regulated expression of the transgene. One example of such a system is the *cre/loxP* recombinase system of bacteriophage P1. For a description of the *cre/loxP* recombinase system, see, *e.g.*, Lakso *et al.* (1992) *Proc. Natl. Acad. Sci. USA* 89:6232-6236. Another example of a recombinase system is the FLP recombinase system of *Saccharomyces cerevisiae* (O'Gorman *et al.*, 1991, *Science* 251:1351-1355). If a *cre/loxP* recombinase system is used to regulate expression of the

transgene, animals containing transgenes encoding both the *Cre* recombinase and a selected protein are required. Such animals can be provided through the construction of "double" transgenic animals, *e.g.*, by mating two transgenic animals, one containing a transgene encoding a selected protein and the other containing a transgene encoding a recombinase.

Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.* (1997) *Nature* 385:810-813 and PCT Publication NOS. WO 97/07668 and WO 97/07669.

10 IV. Pharmaceutical Compositions

The nucleic acid molecules, polypeptides, and antibodies (also referred to herein as "active compounds") of the invention can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the nucleic acid molecule, protein, or antibody and a pharmaceutically acceptable carrier.

15 As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

The invention includes methods for preparing pharmaceutical compositions for modulating the expression or activity of a marker nucleic acid or protein. Such methods comprise formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein. Such compositions can further include additional active agents. Thus, the invention further includes methods for preparing a pharmaceutical composition by formulating a pharmaceutically acceptable carrier with an agent which modulates expression or activity of a marker nucleic acid or protein and one or more additional active compounds.

The invention also provides methods (also referred to herein as "screening assays") for identifying modulators, *i.e.*, candidate or test compounds or agents (*e.g.*, peptides, peptidomimetics, peptoids, small molecules or other drugs) which (a) bind to the marker, or (b) have a modulatory (*e.g.*, stimulatory or inhibitory) effect on the activity of the marker or, more specifically, (c) have a modulatory effect on the interactions of the marker with one or more of its natural substrates (*e.g.*, peptide, protein, hormone, co-factor, or nucleic acid), or (d) have a modulatory effect on the expression of the marker. Such assays typically comprise a reaction between the marker and one or more assay components. The other components may be either the test compound itself, or a combination of test compound and a natural binding partner of the marker.

The test compounds of the present invention may be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. Test compounds may also be obtained by any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; peptoid libraries (libraries of molecules having the functionalities of peptides, but with a novel, non-peptide backbone which are resistant to enzymatic degradation but which nevertheless remain bioactive; see, *e.g.*, Zuckermann *et al.*, 1994, *J. Med. Chem.* 37:2678-85); spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library and peptoid library approaches are limited to peptide libraries, while the other four approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, 1997, *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt *et al.* (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb *et al.* (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann *et al.* (1994). *J. Med. Chem.* 37:2678; Cho *et al.* (1993) *Science* 261:1303; Carrell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carell *et al.* (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and in Gallop *et al.* (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (*e.g.*, Houghten, 1992, *Biotechniques* 13:412-421), or on beads (Lam, 1991, *Nature* 354:82-84), chips (Fodor, 1993, *Nature* 364:555-556), bacteria and/or spores, (Ladner, USP 5,223,409), plasmids (Cull *et al*, 1992, *Proc Natl Acad Sci USA* 89:1865-1869) or on phage (Scott
5 and Smith, 1990, *Science* 249:386-390; Devlin, 1990, *Science* 249:404-406; Cwirla *et al*, 1990, *Proc. Natl. Acad. Sci.* 87:6378-6382; Felici, 1991, *J. Mol. Biol.* 222:301-310; Ladner, *supra.*).

In one embodiment, the invention provides assays for screening candidate or test compounds which are substrates of a protein encoded by or
10 corresponding to a marker or biologically active portion thereof. In another embodiment, the invention provides assays for screening candidate or test compounds which bind to a protein encoded by or corresponding to a marker or biologically active portion thereof. Determining the ability of the test compound to directly bind to a protein can be accomplished, for example, by coupling the compound with a
15 radioisotope or enzymatic label such that binding of the compound to the marker can be determined by detecting the labeled marker compound in a complex. For example, compounds (*e.g.*, marker substrates) can be labeled with ^{125}I , ^{35}S , ^{14}C , or ^3H , either directly or indirectly, and the radioisotope detected by direct counting of radioemission or by scintillation counting. Alternatively, assay components can be enzymatically
20 labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product.

In another embodiment, the invention provides assays for screening candidate or test compounds which modulate the expression of a marker or the activity
25 of a protein encoded by or corresponding to a marker, or a biologically active portion thereof. In all likelihood, the protein encoded by or corresponding to the marker can, *in vivo*, interact with one or more molecules, such as but not limited to, peptides, proteins, hormones, cofactors and nucleic acids. For the purposes of this discussion, such cellular and extracellular molecules are referred to herein as "binding partners" or marker
30 "substrate".

One necessary embodiment of the invention in order to facilitate such screening is the use of a protein encoded by or corresponding to marker to identify the protein's natural *in vivo* binding partners. There are many ways to accomplish this which are known to one skilled in the art. One example is the use of the marker protein as "bait protein" in a two-hybrid assay or three-hybrid assay (see, *e.g.*, U.S. Patent No. 5,283,317; Zervos *et al*, 1993, *Cell* 72:223-232; Madura *et al*, 1993, *J. Biol. Chem.* 268:12046-12054; Bartel *et al*, 1993, *Biotechniques* 14:920-924; Iwabuchi *et al*, 1993 *Oncogene* 8:1693-1696; Brent WO94/10300) in order to identify other proteins which bind to or interact with the marker (binding partners) and, therefore, are possibly involved in the natural function of the marker. Such marker binding partners are also likely to be involved in the propagation of signals by the marker protein or downstream elements of a marker protein-mediated signaling pathway. Alternatively, such marker protein binding partners may also be found to be inhibitors of the marker protein.

The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. In one construct, the gene that encodes a marker protein fused to a gene encoding the DNA binding domain of a known transcription factor (*e.g.*, GAL-4). In the other construct, a DNA sequence, from a library of DNA sequences, that encodes an unidentified protein ("prey" or "sample") is fused to a gene that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact, *in vivo*, forming a marker-dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (*e.g.*, LacZ) which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be readily detected and cell colonies containing the functional transcription factor can be isolated and used to obtain the cloned gene which encodes the protein which interacts with the marker protein.

In a further embodiment, assays may be devised through the use of the invention for the purpose of identifying compounds which modulate (*e.g.*, affect either positively or negatively) interactions between a marker protein and its substrates and/or binding partners. Such compounds can include, but are not limited to, molecules such as antibodies, peptides, hormones, oligonucleotides, nucleic acids, and analogs thereof.

Such compounds may also be obtained from any available source, including systematic libraries of natural and/or synthetic compounds. The preferred assay components for use in this embodiment is an ovarian cancer marker protein identified herein, the known binding partner and/or substrate of same, and the test compound. Test compounds can be
5 supplied from any source.

The basic principle of the assay systems used to identify compounds that interfere with the interaction between the marker protein and its binding partner involves preparing a reaction mixture containing the marker protein and its binding partner under conditions and for a time sufficient to allow the two products to interact
10 and bind, thus forming a complex. In order to test an agent for inhibitory activity, the reaction mixture is prepared in the presence and absence of the test compound. The test compound can be initially included in the reaction mixture, or can be added at a time subsequent to the addition of the marker protein and its binding partner. Control reaction mixtures are incubated without the test compound or with a placebo. The
15 formation of any complexes between the marker protein and its binding partner is then detected. The formation of a complex in the control reaction, but less or no such formation in the reaction mixture containing the test compound, indicates that the compound interferes with the interaction of the marker protein and its binding partner. Conversely, the formation of more complex in the presence of compound than in the
20 control reaction indicates that the compound may enhance interaction of the marker protein and its binding partner.

The assay for compounds that interfere with the interaction of the marker protein with its binding partner may be conducted in a heterogeneous or homogeneous format. Heterogeneous assays involve anchoring either the marker protein or its binding
25 partner onto a solid phase and detecting complexes anchored to the solid phase at the end of the reaction. In homogeneous assays, the entire reaction is carried out in a liquid phase. In either approach, the order of addition of reactants can be varied to obtain different information about the compounds being tested. For example, test compounds that interfere with the interaction between the marker proteins and the binding partners
30 (e.g., by competition) can be identified by conducting the reaction in the presence of the test substance, *i.e.*, by adding the test substance to the reaction mixture prior to or simultaneously with the marker and its interactive binding partner. Alternatively, test

compounds that disrupt preformed complexes, *e.g.*, compounds with higher binding constants that displace one of the components from the complex, can be tested by adding the test compound to the reaction mixture after complexes have been formed. The various formats are briefly described below.

5 In a heterogeneous assay system, either the marker protein or its binding partner is anchored onto a solid surface or matrix, while the other corresponding non-anchored component may be labeled, either directly or indirectly. In practice, microtitre plates are often utilized for this approach. The anchored species can be immobilized by a number of methods, either non-covalent or covalent, that are typically well known to
10 one who practices the art. Non-covalent attachment can often be accomplished simply by coating the solid surface with a solution of the marker protein or its binding partner and drying. Alternatively, an immobilized antibody specific for the assay component to be anchored can be used for this purpose. Such surfaces can often be prepared in advance and stored.

15 In related embodiments, a fusion protein can be provided which adds a domain that allows one or both of the assay components to be anchored to a matrix. For example, glutathione-S-transferase/marker fusion proteins or glutathione-S-transferase/binding partner can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, MO) or glutathione derivatized microtiter plates, which are then
20 combined with the test compound or the test compound and either the non-adsorbed marker or its binding partner, and the mixture incubated under conditions conducive to complex formation (*e.g.*, physiological conditions). Following incubation, the beads or microtiter plate wells are washed to remove any unbound assay components, the immobilized complex assessed either directly or indirectly, for example, as described
25 above. Alternatively, the complexes can be dissociated from the matrix, and the level of marker binding or activity determined using standard techniques.

Other techniques for immobilizing proteins on matrices can also be used in the screening assays of the invention. For example, either a marker protein or a marker protein binding partner can be immobilized utilizing conjugation of biotin and
30 streptavidin. Biotinylated marker protein or target molecules can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of

streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the protein-immobilized surfaces can be prepared in advance and stored.

In order to conduct the assay, the corresponding partner of the immobilized assay component is exposed to the coated surface with or without the test compound. After the reaction is complete, unreacted assay components are removed (e.g., by washing) and any complexes formed will remain immobilized on the solid surface. The detection of complexes anchored on the solid surface can be accomplished in a number of ways. Where the non-immobilized component is pre-labeled, the detection of label immobilized on the surface indicates that complexes were formed. Where the non-immobilized component is not pre-labeled, an indirect label can be used to detect complexes anchored on the surface; e.g., using a labeled antibody specific for the initially non-immobilized species (the antibody, in turn, can be directly labeled or indirectly labeled with, e.g., a labeled anti-Ig antibody). Depending upon the order of addition of reaction components, test compounds which modulate (inhibit or enhance) complex formation or which disrupt preformed complexes can be detected.

In an alternate embodiment of the invention, a homogeneous assay may be used. This is typically a reaction, analogous to those mentioned above, which is conducted in a liquid phase in the presence or absence of the test compound. The formed complexes are then separated from unreacted components, and the amount of complex formed is determined. As mentioned for heterogeneous assay systems, the order of addition of reactants to the liquid phase can yield information about which test compounds modulate (inhibit or enhance) complex formation and which disrupt preformed complexes.

In such a homogeneous assay, the reaction products may be separated from unreacted assay components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, complexes of molecules may be separated from uncomplexed molecules through a series of centrifugal steps, due to the different sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., *Trends Biochem Sci* 1993 Aug;18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration

chromatography separates molecules based on size, and through the utilization of an appropriate gel filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the complex as compared to the uncomplexed molecules may be exploited to differentially separate the complex from the remaining individual reactants, for example through the use of ion-exchange chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.*, Heegaard, 1998, *J Mol. Recognit.* 11:141-148; Hage and Tweed, 1997, *J. Chromatogr. B. Biomed. Sci. Appl.*, 699:499-525). Gel electrophoresis may also be employed to separate complexed molecules from unbound species (see, *e.g.*, Ausubel *et al* (eds.), as described in : Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the electrophoretic process, nondenaturing gels in the absence of reducing agent are typically preferred, but conditions appropriate to the particular interactants will be well known to one skilled in the art. Immunoprecipitation is another common technique utilized for the isolation of a protein-protein complex from solution (see, *e.g.*, Ausubel *et al* (eds.), In: Current Protocols in Molecular Biology, J. Wiley & Sons, New York. 1999). In this technique, all proteins binding to an antibody specific to one of the binding molecules are precipitated from solution by conjugating the antibody to a polymer bead that may be readily collected by centrifugation. The bound assay components are released from the beads (through a specific proteolysis event or other technique well known in the art which will not disturb the protein-protein interaction in the complex), and a second immunoprecipitation step is performed, this time utilizing antibodies specific for the correspondingly different interacting assay component. In this manner, only formed complexes should remain attached to the beads. Variations in complex formation in both the presence and the absence of a test compound can be compared, thus offering information about the ability of the compound to modulate interactions between the marker protein and its binding partner.

Also within the scope of the present invention are methods for direct detection of interactions between the marker protein and its natural binding partner and/or a test compound in a homogeneous or heterogeneous assay system without

further sample manipulation. For example, the technique of fluorescence energy transfer may be utilized (see, *e.g.*, Lakowicz *et al*, U.S. Patent No. 5,631,169; Stavrianopoulos *et al*, U.S. Patent No. 4,868,103). Generally, this technique involves the addition of a fluorophore label on a first 'donor' molecule (*e.g.*, marker or test compound) such that its emitted fluorescent energy will be absorbed by a fluorescent label on a second, 'acceptor' molecule (*e.g.*, marker or test compound), which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter). A test substance which either enhances or hinders participation of one of the species in the preformed complex will result in the generation of a signal variant to that of background. In this way, test substances that modulate interactions between a marker and its binding partner can be identified in controlled assays.

In another embodiment, modulators of marker expression are identified in a method wherein a cell is contacted with a candidate compound and the expression of marker mRNA or protein in the cell, is determined. The level of expression of marker mRNA or protein in the presence of the candidate compound is compared to the level of expression of marker mRNA or protein in the absence of the candidate compound. The candidate compound can then be identified as a modulator of marker expression based on this comparison. For example, when expression of marker mRNA or protein is greater (statistically significantly greater) in the presence of the candidate compound than in its absence, the candidate compound is identified as a stimulator of marker mRNA or protein expression. Conversely, when expression of marker mRNA or protein is less (statistically significantly less) in the presence of the candidate compound than in its absence, the candidate compound is identified as an inhibitor of marker mRNA or protein expression. The level of marker mRNA or protein expression

in the cells can be determined by methods described herein for detecting marker mRNA or protein.

In another aspect, the invention pertains to a combination of two or more of the assays described herein. For example, a modulating agent can be identified using
5 a cell-based or a cell free assay, and the ability of the agent to modulate the activity of a marker protein can be further confirmed *in vivo*, *e.g.*, in a whole animal model for cellular transformation and/or tumorigenesis.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to
10 further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, an marker modulating agent, an antisense marker nucleic acid molecule, an marker-specific antibody, or an marker-binding partner) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as
15 described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein.

It is understood that appropriate doses of small molecule agents and protein or polypeptide agents depends upon a number of factors within the knowledge of
20 the ordinarily skilled physician, veterinarian, or researcher. The dose(s) of these agents will vary, for example, depending upon the identity, size, and condition of the subject or sample being treated, further depending upon the route by which the composition is to be administered, if applicable, and the effect which the practitioner desires the agent to have upon the nucleic acid or polypeptide of the invention. Exemplary doses of a small
25 molecule include milligram or microgram amounts per kilogram of subject or sample weight (*e.g.* about 1 microgram per kilogram to about 500 milligrams per kilogram, about 100 micrograms per kilogram to about 5 milligrams per kilogram, or about 1 microgram per kilogram to about 50 micrograms per kilogram). Exemplary doses of a protein or polypeptide include gram, milligram or microgram amounts per kilogram of
30 subject or sample weight (*e.g.* about 1 microgram per kilogram to about 5 grams per kilogram, about 100 micrograms per kilogram to about 500 milligrams per kilogram, or about 1 milligram per kilogram to about 50 milligrams per kilogram). It is furthermore

understood that appropriate doses of one of these agents depend upon the potency of the agent with respect to the expression or activity to be modulated. Such appropriate doses can be determined using the assays described herein. When one or more of these agents is to be administered to an animal (*e.g.* a human) in order to modulate expression or activity of a polypeptide or nucleic acid of the invention, a physician, veterinarian, or researcher can, for example, prescribe a relatively low dose at first, subsequently increasing the dose until an appropriate response is obtained. In addition, it is understood that the specific dose level for any particular animal subject will depend upon a variety of factors including the activity of the specific agent employed, the age, body weight, general health, gender, and diet of the subject, the time of administration, the route of administration, the rate of excretion, any drug combination, and the degree of expression or activity to be modulated.

A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediamine-tetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL (BASF; Parsippany, NJ) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy

syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid
5 polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid,
10 thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

15 Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, a polypeptide or antibody) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium,
20 and then incorporating the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

25 Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid
30 carrier is applied orally and swished and expectorated or swallowed.

Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches, and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a
5 lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

For administration by inhalation, the compounds are delivered in the
10 form of an aerosol spray from a pressurized container or dispenser which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally
15 known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

20 The compounds can also be prepared in the form of suppositories (*e.g.*, with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled
25 release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova
30 Pharmaceuticals, Inc. Liposomal suspensions (including liposomes having monoclonal antibodies incorporated therein or thereon) can also be used as pharmaceutically

acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811.

It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit
5 form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound
10 and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

For antibodies, the preferred dosage is 0.1 mg/kg to 100 mg/kg of body weight (generally 10 mg/kg to 20 mg/kg). If the antibody is to act in the brain, a dosage of 50 mg/kg to 100 mg/kg is usually appropriate. Generally, partially human antibodies
15 and fully human antibodies have a longer half-life within the human body than other antibodies. Accordingly, lower dosages and less frequent administration is often possible. Modifications such as lipidation can be used to stabilize antibodies and to enhance uptake and tissue penetration (*e.g.*, into the ovarian epithelium). A method for lipidation of antibodies is described by Cruikshank *et al.* (1997) *J. Acquired Immune*
20 *Deficiency Syndromes and Human Retrovirology* 14:193.

The invention also provides vaccine compositions for the prevention and/or treatment of ovarian cancer. The invention provides ovarian cancer vaccine compositions in which a protein of a marker of Table 1, or a combination of proteins of the markers of Table 1, are introduced into a subject in order to stimulate an immune
25 response against the ovarian cancer. The invention also provides ovarian cancer vaccine compositions in which a gene expression construct, which expresses a marker or fragment of a marker identified in Table 1, is introduced into the subject such that a protein or fragment of a protein encoded by a marker of Table 1 is produced by transfected cells in the subject at a higher than normal level and elicits an immune
30 response.

In one embodiment, an ovarian cancer vaccine is provided and employed as an immunotherapeutic agent for the prevention of ovarian cancer. In another embodiment, an ovarian cancer vaccine is provided and employed as an immunotherapeutic agent for the treatment of ovarian cancer.

5 By way of example, an ovarian cancer vaccine comprised of the proteins of the markers of Table 1, may be employed for the prevention and/or treatment of ovarian cancer in a subject by administering the vaccine by a variety of routes, *e.g.*, intradermally, subcutaneously, or intramuscularly. In addition, the ovarian cancer vaccine can be administered together with adjuvants and/or immunomodulators to boost
10 the activity of the vaccine and the subject's response. In one embodiment, devices and/or compositions containing the vaccine, suitable for sustained or intermittent release could be, implanted in the body or topically applied thereto for the relatively slow release of such materials into the body. The ovarian cancer vaccine can be introduced along with immunomodulatory compounds, which can alter the type of immune
15 response produced in order to produce a response which will be more effective in eliminating the cancer.

In another embodiment, an ovarian cancer vaccine comprised of an expression construct of the markers of Table 1, may be introduced by injection into muscle or by coating onto microprojectiles and using a device designed for the purpose
20 to fire the projectiles at high speed into the skin. The cells of the subject will then express the protein(s) or fragments of proteins of the markers of Table 1 and induce an immune response. In addition, the ovarian cancer vaccine may be introduced along with expression constructs for immunomodulatory molecules, such as cytokines, which may increase the immune response or modulate the type of immune response produced in
25 order to produce a response which will be more effective in eliminating the cancer.

The marker nucleic acid molecules of the present invention can also be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470), or by stereotactic injection (see, *e.g.*, Chen *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* 91:3054-3057). The pharmaceutical preparation of the gene therapy
30 vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded. Alternatively,

where the complete gene delivery vector can be produced intact from recombinant cells, *e.g.* retroviral vectors, the pharmaceutical preparation can include one or more cells which produce the gene delivery system.

The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

V. Predictive Medicine

The present invention pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trails are used for prognostic (predictive) purposes to thereby treat an individual prophylactically. Accordingly, one aspect of the present invention relates to diagnostic assays for determining the level of expression of one or more marker proteins or nucleic acids, in order to determine whether an individual is at risk of developing ovarian cancer. Such assays can be used for prognostic or predictive purposes to thereby prophylactically treat an individual prior to the onset of the cancer.

Yet another aspect of the invention pertains to monitoring the influence of agents (*e.g.*, drugs or other compounds administered either to inhibit ovarian cancer or to treat or prevent any other disorder {*i.e.* in order to understand any ovarian carcinogenic effects that such treatment may have}) on the expression or activity of a marker of the invention in clinical trials. These and other agents are described in further detail in the following sections.

A. Diagnostic Assays

An exemplary method for detecting the presence or absence of a marker protein or nucleic acid in a biological sample involves obtaining a biological sample (*e.g.* an ovary-associated body fluid) from a test subject and contacting the biological sample with a compound or an agent capable of detecting the polypeptide or nucleic acid (*e.g.*, mRNA, genomic DNA, or cDNA). The detection methods of the invention can thus be used to detect mRNA, protein, cDNA, or genomic DNA, for example, in a biological sample *in vitro* as well as *in vivo*. For example, *in vitro* techniques for detection of mRNA include Northern hybridizations and *in situ* hybridizations. *In vitro* techniques for detection of a marker protein include enzyme linked immunosorbent

assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. *In vitro* techniques for detection of genomic DNA include Southern hybridizations. Furthermore, *in vivo* techniques for detection of a marker protein include introducing into a subject a labeled antibody directed against the protein or fragment thereof. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

A general principle of such diagnostic and prognostic assays involves preparing a sample or reaction mixture that may contain a marker, and a probe, under appropriate conditions and for a time sufficient to allow the marker and probe to interact and bind, thus forming a complex that can be removed and/or detected in the reaction mixture. These assays can be conducted in a variety of ways.

For example, one method to conduct such an assay would involve anchoring the marker or probe onto a solid phase support, also referred to as a substrate, and detecting target marker/probe complexes anchored on the solid phase at the end of the reaction. In one embodiment of such a method, a sample from a subject, which is to be assayed for presence and/or concentration of marker, can be anchored onto a carrier or solid phase support. In another embodiment, the reverse situation is possible, in which the probe can be anchored to a solid phase and a sample from a subject can be allowed to react as an unanchored component of the assay.

There are many established methods for anchoring assay components to a solid phase. These include, without limitation, marker or probe molecules which are immobilized through conjugation of biotin and streptavidin. Such biotinylated assay components can be prepared from biotin-NHS (N-hydroxy-succinimide) using techniques known in the art (*e.g.*, biotinylation kit, Pierce Chemicals, Rockford, IL), and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). In certain embodiments, the surfaces with immobilized assay components can be prepared in advance and stored.

Other suitable carriers or solid phase supports for such assays include any material capable of binding the class of molecule to which the marker or probe belongs. Well-known supports or carriers include, but are not limited to, glass, polystyrene, nylon, polypropylene, nylon, polyethylene, dextran, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

In order to conduct assays with the above mentioned approaches, the non-immobilized component is added to the solid phase upon which the second component is anchored. After the reaction is complete, uncomplexed components may be removed (*e.g.*, by washing) under conditions such that any complexes formed will remain immobilized upon the solid phase. The detection of marker/probe complexes anchored to the solid phase can be accomplished in a number of methods outlined herein.

In a preferred embodiment, the probe, when it is the unanchored assay component, can be labeled for the purpose of detection and readout of the assay, either directly or indirectly, with detectable labels discussed herein and which are well-known to one skilled in the art.

It is also possible to directly detect marker/probe complex formation without further manipulation or labeling of either component (marker or probe), for example by utilizing the technique of fluorescence energy transfer (see, for example, Lakowicz *et al.*, U.S. Patent No. 5,631,169; Stavrianopoulos, *et al.*, U.S. Patent No. 4,868,103). A fluorophore label on the first, 'donor' molecule is selected such that, upon excitation with incident light of appropriate wavelength, its emitted fluorescent energy will be absorbed by a fluorescent label on a second 'acceptor' molecule, which in turn is able to fluoresce due to the absorbed energy. Alternately, the 'donor' protein molecule may simply utilize the natural fluorescent energy of tryptophan residues. Labels are chosen that emit different wavelengths of light, such that the 'acceptor' molecule label may be differentiated from that of the 'donor'. Since the efficiency of energy transfer between the labels is related to the distance separating the molecules, spatial relationships between the molecules can be assessed. In a situation in which binding occurs between the molecules, the fluorescent emission of the 'acceptor' molecule label in the assay should be maximal. An FET binding event can be conveniently measured through standard fluorometric detection means well known in the art (*e.g.*, using a fluorimeter).

In another embodiment, determination of the ability of a probe to recognize a marker can be accomplished without labeling either assay component (probe or marker) by utilizing a technology such as real-time Biomolecular Interaction Analysis (BIA) (see, *e.g.*, Sjolander, S. and Urbaniczky, C., 1991, *Anal. Chem.* 63:2338-2345

and Szabo *et al.*, 1995, *Curr. Opin. Struct. Biol.* 5:699-705). As used herein, "BIA" or "surface plasmon resonance" is a technology for studying biospecific interactions in real time, without labeling any of the interactants (*e.g.*, BIAcore). Changes in the mass at the binding surface (indicative of a binding event) result in alterations of the refractive index of light near the surface (the optical phenomenon of surface plasmon resonance (SPR)),
5 resulting in a detectable signal which can be used as an indication of real-time reactions between biological molecules.

Alternatively, in another embodiment, analogous diagnostic and prognostic assays can be conducted with marker and probe as solutes in a liquid phase.

10 In such an assay, the complexed marker and probe are separated from uncomplexed components by any of a number of standard techniques, including but not limited to: differential centrifugation, chromatography, electrophoresis and immunoprecipitation. In differential centrifugation, marker/probe complexes may be separated from uncomplexed assay components through a series of centrifugal steps, due to the different
15 sedimentation equilibria of complexes based on their different sizes and densities (see, for example, Rivas, G., and Minton, A.P., 1993, *Trends Biochem Sci.* 18(8):284-7). Standard chromatographic techniques may also be utilized to separate complexed molecules from uncomplexed ones. For example, gel filtration chromatography separates molecules based on size, and through the utilization of an appropriate gel
20 filtration resin in a column format, for example, the relatively larger complex may be separated from the relatively smaller uncomplexed components. Similarly, the relatively different charge properties of the marker/probe complex as compared to the uncomplexed components may be exploited to differentiate the complex from uncomplexed components, for example through the utilization of ion-exchange
25 chromatography resins. Such resins and chromatographic techniques are well known to one skilled in the art (see, *e.g.*, Heegaard, N.H., 1998, *J. Mol. Recognit.* Winter 11(1-6):141-8; Hage, D.S., and Tweed, S.A. *J Chromatogr B Biomed Sci Appl* 1997 Oct 10;699(1-2):499-525). Gel electrophoresis may also be employed to separate complexed assay components from unbound components (see, *e.g.*, Ausubel *et al.*, ed.,
30 *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, 1987-1999). In this technique, protein or nucleic acid complexes are separated based on size or charge, for example. In order to maintain the binding interaction during the

electrophoretic process, non-denaturing gel matrix materials and conditions in the absence of reducing agent are typically preferred. Appropriate conditions to the particular assay and components thereof will be well known to one skilled in the art.

In a particular embodiment, the level of marker mRNA can be
5 determined both by *in situ* and by *in vitro* formats in a biological sample using methods known in the art. The term "biological sample" is intended to include tissues, cells, biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and fluids present within a subject. Many expression detection methods use isolated RNA. For *in vitro* methods, any RNA isolation technique that does not select against the
10 isolation of mRNA can be utilized for the purification of RNA from ovarian cells (see, e.g., Ausubel *et al.*, ed., *Current Protocols in Molecular Biology*, John Wiley & Sons, New York 1987-1999). Additionally, large numbers of tissue samples can readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski (1989, U.S. Patent No.
15 4,843,155).

The isolated mRNA can be used in hybridization or amplification assays that include, but are not limited to, Southern or Northern analyses, polymerase chain reaction analyses and probe arrays. One preferred diagnostic method for the detection of mRNA levels involves contacting the isolated mRNA with a nucleic acid molecule
20 (probe) that can hybridize to the mRNA encoded by the gene being detected. The nucleic acid probe can be, for example, a full-length cDNA, or a portion thereof, such as an oligonucleotide of at least 7, 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to a mRNA or genomic DNA encoding a marker of the present invention. Other suitable probes for use in the
25 diagnostic assays of the invention are described herein. Hybridization of an mRNA with the probe indicates that the marker in question is being expressed.

In one format, the mRNA is immobilized on a solid surface and contacted with a probe, for example by running the isolated mRNA on an agarose gel and transferring the mRNA from the gel to a membrane, such as nitrocellulose. In an
30 alternative format, the probe(s) are immobilized on a solid surface and the mRNA is contacted with the probe(s), for example, in an Affymetrix gene chip array. A skilled

artisan can readily adapt known mRNA detection methods for use in detecting the level of mRNA encoded by the markers of the present invention.

An alternative method for determining the level of mRNA marker in a sample involves the process of nucleic acid amplification, *e.g.*, by rtPCR (the
5 experimental embodiment set forth in Mullis, 1987, U.S. Patent No. 4,683,202), ligase chain reaction (Barany, 1991, *Proc. Natl. Acad. Sci. USA*, 88:189-193), self sustained sequence replication (Guatelli *et al.*, 1990, *Proc. Natl. Acad. Sci. USA* 87:1874-1878), transcriptional amplification system (Kwoh *et al.*, 1989, *Proc. Natl. Acad. Sci. USA* 86:1173-1177), Q-Beta Replicase (Lizardi *et al.*, 1988, *Bio/Technology* 6:1197), rolling
10 circle replication (Lizardi *et al.*, U.S. Patent No. 5,854,033) or any other nucleic acid amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of nucleic acid molecules if such molecules are present in very low numbers. As used herein, amplification primers are defined as being
15 a pair of nucleic acid molecules that can anneal to 5' or 3' regions of a gene (plus and minus strands, respectively, or vice-versa) and contain a short region in between. In general, amplification primers are from about 10 to 30 nucleotides in length and flank a region from about 50 to 200 nucleotides in length. Under appropriate conditions and with appropriate reagents, such primers permit the amplification of a nucleic acid
20 molecule comprising the nucleotide sequence flanked by the primers.

For *in situ* methods, mRNA does not need to be isolated from the ovarian cells prior to detection. In such methods, a cell or tissue sample is prepared/processed using known histological methods. The sample is then immobilized on a support, typically a glass slide, and then contacted with a probe that can hybridize to mRNA that
25 encodes the marker.

As an alternative to making determinations based on the absolute expression level of the marker, determinations may be based on the normalized expression level of the marker. Expression levels are normalized by correcting the absolute expression level of a marker by comparing its expression to the expression of a
30 gene that is not a marker, *e.g.*, a housekeeping gene that is constitutively expressed. Suitable genes for normalization include housekeeping genes such as the actin gene, or epithelial cell-specific genes. This normalization allows the comparison of the

expression level in one sample, *e.g.*, a patient sample, to another sample, *e.g.*, a non-ovarian cancer sample, or between samples from different sources.

Alternatively, the expression level can be provided as a relative expression level. To determine a relative expression level of a marker, the level of
5 expression of the marker is determined for 10 or more samples of normal versus cancer cell isolates, preferably 50 or more samples, prior to the determination of the expression level for the sample in question. The mean expression level of each of the genes assayed in the larger number of samples is determined and this is used as a baseline expression level for the marker. The expression level of the marker determined for the
10 test sample (absolute level of expression) is then divided by the mean expression value obtained for that marker. This provides a relative expression level.

Preferably, the samples used in the baseline determination will be from ovarian cancer or from non-ovarian cancer cells of ovarian tissue. The choice of the cell source is dependent on the use of the relative expression level. Using expression found
15 in normal tissues as a mean expression score aids in validating whether the marker assayed is ovarian specific (versus normal cells). In addition, as more data is accumulated, the mean expression value can be revised, providing improved relative expression values based on accumulated data. Expression data from ovarian cells provides a means for grading the severity of the ovarian cancer state.

20 In another embodiment of the present invention, a marker protein is detected. A preferred agent for detecting marker protein of the invention is an antibody capable of binding to such a protein or a fragment thereof, preferably an antibody with a detectable label. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment or derivatives thereof (*e.g.*, Fab or F(ab')₂) can be used.
25 The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody
30 and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

Proteins from ovarian cells can be isolated using techniques that are well known to those of skill in the art. The protein isolation methods employed can, for example, be such as those described in Harlow and Lane (Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York).

A variety of formats can be employed to determine whether a sample contains a protein that binds to a given antibody. Examples of such formats include, but are not limited to, enzyme immunoassay (EIA), radioimmunoassay (RIA), Western blot analysis and enzyme linked immunoabsorbant assay (ELISA). A skilled artisan can readily adapt known protein/antibody detection methods for use in determining whether ovarian cells express a marker of the present invention.

In one format, antibodies, or antibody fragments or derivatives, can be used in methods such as Western blots or immunofluorescence techniques to detect the expressed proteins. In such uses, it is generally preferable to immobilize either the antibody or proteins on a solid support. Suitable solid phase supports or carriers include any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite.

One skilled in the art will know many other suitable carriers for binding antibody or antigen, and will be able to adapt such support for use with the present invention. For example, protein isolated from ovarian cells can be run on a polyacrylamide gel electrophoresis and immobilized onto a solid phase support such as nitrocellulose. The support can then be washed with suitable buffers followed by treatment with the detectably labeled antibody. The solid phase support can then be washed with the buffer a second time to remove unbound antibody. The amount of bound label on the solid support can then be detected by conventional means.

The invention also encompasses kits for detecting the presence of a marker protein or nucleic acid in a biological sample (*e.g.* an ovary-associated body fluid such as a urine sample). Such kits can be used to determine if a subject is suffering from or is at increased risk of developing ovarian cancer. For example, the kit can comprise a labeled compound or agent capable of detecting a marker protein or nucleic acid in a biological sample and means for determining the amount of the protein or

mRNA in the sample (*e.g.*, an antibody which binds the protein or a fragment thereof, or an oligonucleotide probe which binds to DNA or mRNA encoding the protein). Kits can also include instructions for interpreting the results obtained using the kit.

For antibody-based kits, the kit can comprise, for example: (1) a first
5 antibody (*e.g.*, attached to a solid support) which binds to a marker protein; and, optionally, (2) a second, different antibody which binds to either the protein or the first antibody and is conjugated to a detectable label.

For oligonucleotide-based kits, the kit can comprise, for example: (1) an oligonucleotide, *e.g.*, a detectably labeled oligonucleotide, which hybridizes to a nucleic
10 acid sequence encoding a marker protein or (2) a pair of primers useful for amplifying a marker nucleic acid molecule. The kit can also comprise, *e.g.*, a buffering agent, a preservative, or a protein stabilizing agent. The kit can further comprise components necessary for detecting the detectable label (*e.g.*, an enzyme or a substrate). The kit can
15 also contain a control sample or a series of control samples which can be assayed and compared to the test sample. Each component of the kit can be enclosed within an individual container and all of the various containers can be within a single package, along with instructions for interpreting the results of the assays performed using the kit.

B. Pharmacogenomics

20 Agents or modulators which have a stimulatory or inhibitory effect on expression of a marker of the invention can be administered to individuals to treat (prophylactically or therapeutically) ovarian cancer in the patient. In conjunction with such treatment, the pharmacogenomics (*i.e.*, the study of the relationship between an individual's genotype and that individual's response to a foreign compound or drug) of
25 the individual may be considered. Differences in metabolism of therapeutics can lead to severe toxicity or therapeutic failure by altering the relation between dose and blood concentration of the pharmacologically active drug. Thus, the pharmacogenomics of the individual permits the selection of effective agents (*e.g.*, drugs) for prophylactic or therapeutic treatments based on a consideration of the individual's genotype. Such
30 pharmacogenomics can further be used to determine appropriate dosages and therapeutic regimens. Accordingly, the level of expression of a marker of the invention in an

individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual.

Pharmacogenomics deals with clinically significant variations in the response to drugs due to altered drug disposition and abnormal action in affected persons. See, *e.g.*, Linder (1997) *Clin. Chem.* 43(2):254-266. In general, two types of pharmacogenetic conditions can be differentiated. Genetic conditions transmitted as a single factor altering the way drugs act on the body are referred to as "altered drug action." Genetic conditions transmitted as single factors altering the way the body acts on drugs are referred to as "altered drug metabolism". These pharmacogenetic conditions can occur either as rare defects or as polymorphisms. For example, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common inherited enzymopathy in which the main clinical complication is hemolysis after ingestion of oxidant drugs (anti-malarials, sulfonamides, analgesics, nitrofurans) and consumption of fava beans.

As an illustrative embodiment, the activity of drug metabolizing enzymes is a major determinant of both the intensity and duration of drug action. The discovery of genetic polymorphisms of drug metabolizing enzymes (*e.g.*, N-acetyltransferase 2 (NAT 2) and cytochrome P450 enzymes CYP2D6 and CYP2C19) has provided an explanation as to why some patients do not obtain the expected drug effects or show exaggerated drug response and serious toxicity after taking the standard and safe dose of a drug. These polymorphisms are expressed in two phenotypes in the population, the extensive metabolizer (EM) and poor metabolizer (PM). The prevalence of PM is different among different populations. For example, the gene coding for CYP2D6 is highly polymorphic and several mutations have been identified in PM, which all lead to the absence of functional CYP2D6. Poor metabolizers of CYP2D6 and CYP2C19 quite frequently experience exaggerated drug response and side effects when they receive standard doses. If a metabolite is the active therapeutic moiety, a PM will show no therapeutic response, as demonstrated for the analgesic effect of codeine mediated by its CYP2D6-formed metabolite morphine. The other extreme are the so called ultra-rapid metabolizers who do not respond to standard doses. Recently, the molecular basis of ultra-rapid metabolism has been identified to be due to CYP2D6 gene amplification.

Thus, the level of expression of a marker of the invention in an individual can be determined to thereby select appropriate agent(s) for therapeutic or prophylactic treatment of the individual. In addition, pharmacogenetic studies can be used to apply genotyping of polymorphic alleles encoding drug-metabolizing enzymes to the
5 identification of an individual's drug responsiveness phenotype. This knowledge, when applied to dosing or drug selection, can avoid adverse reactions or therapeutic failure and thus enhance therapeutic or prophylactic efficiency when treating a subject with a modulator of expression of a marker of the invention.

10 C. Monitoring Clinical Trials

Monitoring the influence of agents (*e.g.*, drug compounds) on the level of expression of a marker of the invention can be applied not only in basic drug screening, but also in clinical trials. For example, the effectiveness of an agent to affect marker expression can be monitored in clinical trials of subjects receiving treatment for ovarian
15 cancer. In a preferred embodiment, the present invention provides a method for monitoring the effectiveness of treatment of a subject with an agent (*e.g.*, an agonist, antagonist, peptidomimetic, protein, peptide, nucleic acid, small molecule, or other drug candidate) comprising the steps of (i) obtaining a pre-administration sample from a subject prior to administration of the agent; (ii) detecting the level of expression of one
20 or more selected markers of the invention in the pre-administration sample; (iii) obtaining one or more post-administration samples from the subject; (iv) detecting the level of expression of the marker(s) in the post-administration samples; (v) comparing the level of expression of the marker(s) in the pre-administration sample with the level of expression of the marker(s) in the post-administration sample or samples; and (vi)
25 altering the administration of the agent to the subject accordingly. For example, increased administration of the agent can be desirable to increase expression of the marker(s) to higher levels than detected, *i.e.*, to increase the effectiveness of the agent. Alternatively, decreased administration of the agent can be desirable to decrease expression of the marker(s) to lower levels than detected, *i.e.*, to decrease the
30 effectiveness of the agent.

D. Electronic Apparatus Readable Media and Arrays

Electronic apparatus readable media comprising a marker of the present invention is also provided. As used herein, "electronic apparatus readable media" refers to any suitable medium for storing, holding or containing data or information that can be
5 read and accessed directly by an electronic apparatus. Such media can include, but are not limited to: magnetic storage media, such as floppy discs, hard disc storage medium, and magnetic tape; optical storage media such as compact disc; electronic storage media such as RAM, ROM, EPROM, EEPROM and the like; general hard disks and hybrids of these categories such as magnetic/optical storage media. The medium is adapted or
10 configured for having recorded thereon a marker of the present invention.

As used herein, the term "electronic apparatus" is intended to include any suitable computing or processing apparatus or other device configured or adapted for storing data or information. Examples of electronic apparatus suitable for use with the present invention include stand-alone computing apparatus; networks, including a local
15 area network (LAN), a wide area network (WAN) Internet, Intranet, and Extranet; electronic appliances such as a personal digital assistants (PDAs), cellular phone, pager and the like; and local and distributed processing systems.

As used herein, "recorded" refers to a process for storing or encoding information on the electronic apparatus readable medium. Those skilled in the art can
20 readily adopt any of the presently known methods for recording information on known media to generate manufactures comprising the markers of the present invention.

A variety of software programs and formats can be used to store the marker information of the present invention on the electronic apparatus readable medium. For example, the marker nucleic acid sequence can be represented in a word
25 processing text file, formatted in commercially-available software such as WordPerfect and MicroSoft Word, or represented in the form of an ASCII file, stored in a database application, such as DB2, Sybase, Oracle, or the like, as well as in other forms. Any number of data processor structuring formats (*e.g.*, text file or database) may be employed in order to obtain or create a medium having recorded thereon the the markers
30 of the present invention.

By providing the markers of the invention in readable form, one can routinely access the marker sequence information for a variety of purposes. For example, one skilled in the art can use the nucleotide or amino acid sequences of the present invention in readable form to compare a target sequence or target structural motif with the sequence information stored within the data storage means. Search means are used to identify fragments or regions of the sequences of the invention which match a particular target sequence or target motif.

The present invention therefore provides a medium for holding instructions for performing a method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer, wherein the method comprises the steps of determining the presence or absence of a marker and based on the presence or absence of the marker, determining whether the subject has ovarian cancer or a pre-disposition to ovarian cancer and/or recommending a particular treatment for ovarian cancer or pre-ovarian cancer condition.

The present invention further provides in an electronic system and/or in a network, a method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer associated with a marker wherein the method comprises the steps of determining the presence or absence of the marker, and based on the presence or absence of the marker, determining whether the subject has ovarian cancer or a pre-disposition to ovarian cancer, and/or recommending a particular treatment for the ovarian cancer or pre-ovarian cancer condition. The method may further comprise the step of receiving phenotypic information associated with the subject and/or acquiring from a network phenotypic information associated with the subject.

The present invention also provides in a network, a method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer associated with a marker, said method comprising the steps of receiving information associated with the marker receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or ovarian cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has a ovarian cancer or a pre-disposition to ovarian cancer. The method may further comprise the step of

recommending a particular treatment for the ovarian cancer or pre-ovarian cancer condition.

The present invention also provides a business method for determining whether a subject has ovarian cancer or a pre-disposition to ovarian cancer, said method comprising the steps of receiving information associated with the marker, receiving phenotypic information associated with the subject, acquiring information from the network corresponding to the marker and/or ovarian cancer, and based on one or more of the phenotypic information, the marker, and the acquired information, determining whether the subject has ovarian cancer or a pre-disposition to ovarian cancer. The method may further comprise the step of recommending a particular treatment for the ovarian cancer or pre-ovarian cancer condition.

The invention also includes an array comprising a marker of the present invention. The array can be used to assay expression of one or more genes in the array. In one embodiment, the array can be used to assay gene expression in a tissue to ascertain tissue specificity of genes in the array. In this manner, up to about 7600 genes can be simultaneously assayed for expression. This allows a profile to be developed showing a battery of genes specifically expressed in one or more tissues.

In addition to such qualitative determination, the invention allows the quantitation of gene expression. Thus, not only tissue specificity, but also the level of expression of a battery of genes in the tissue is ascertainable. Thus, genes can be grouped on the basis of their tissue expression *per se* and level of expression in that tissue. This is useful, for example, in ascertaining the relationship of gene expression between or among tissues. Thus, one tissue can be perturbed and the effect on gene expression in a second tissue can be determined. In this context, the effect of one cell type on another cell type in response to a biological stimulus can be determined. Such a determination is useful, for example, to know the effect of cell-cell interaction at the level of gene expression. If an agent is administered therapeutically to treat one cell type but has an undesirable effect on another cell type, the invention provides an assay to determine the molecular basis of the undesirable effect and thus provides the opportunity to co-administer a counteracting agent or otherwise treat the undesired effect. Similarly, even within a single cell type, undesirable biological effects can be

determined at the molecular level. Thus, the effects of an agent on expression of other than the target gene can be ascertained and counteracted.

In another embodiment, the array can be used to monitor the time course of expression of one or more genes in the array. This can occur in various biological contexts, as disclosed herein, for example development of ovarian cancer, progression of ovarian cancer, and processes, such a cellular transformation associated with ovarian cancer.

The array is also useful for ascertaining the effect of the expression of a gene on the expression of other genes in the same cell or in different cells. This provides, for example, for a selection of alternate molecular targets for therapeutic intervention if the ultimate or downstream target cannot be regulated.

The array is also useful for ascertaining differential expression patterns of one or more genes in normal and abnormal cells. This provides a battery of genes that could serve as a molecular target for diagnosis or therapeutic intervention.

15

E. Surrogate Markers

The markers of the invention may serve as surrogate markers for one or more disorders or disease states or for conditions leading up to disease states, and in particular, ovarian cancer. As used herein, a "surrogate marker" is an objective biochemical marker which correlates with the absence or presence of a disease or disorder, or with the progression of a disease or disorder (*e.g.*, with the presence or absence of a tumor). The presence or quantity of such markers is independent of the disease. Therefore, these markers may serve to indicate whether a particular course of treatment is effective in lessening a disease state or disorder. Surrogate markers are of particular use when the presence or extent of a disease state or disorder is difficult to assess through standard methodologies (*e.g.*, early stage tumors), or when an assessment of disease progression is desired before a potentially dangerous clinical endpoint is reached (*e.g.*, an assessment of cardiovascular disease may be made using cholesterol levels as a surrogate marker, and an analysis of HIV infection may be made using HIV RNA levels as a surrogate marker, well in advance of the undesirable clinical outcomes of myocardial infarction or fully-developed AIDS). Examples of the use of surrogate

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25
30

markers in the art include: Koomen *et al.* (2000) *J. Mass. Spectrom.* 35: 258-264; and James (1994) *AIDS Treatment News Archive* 209.

The markers of the invention are also useful as pharmacodynamic markers. As used herein, a "pharmacodynamic marker" is an objective biochemical marker which correlates specifically with drug effects. The presence or quantity of a pharmacodynamic marker is not related to the disease state or disorder for which the drug is being administered; therefore, the presence or quantity of the marker is indicative of the presence or activity of the drug in a subject. For example, a pharmacodynamic marker may be indicative of the concentration of the drug in a biological tissue, in that the marker is either expressed or transcribed or not expressed or transcribed in that tissue in relationship to the level of the drug. In this fashion, the distribution or uptake of the drug may be monitored by the pharmacodynamic marker. Similarly, the presence or quantity of the pharmacodynamic marker may be related to the presence or quantity of the metabolic product of a drug, such that the presence or quantity of the marker is indicative of the relative breakdown rate of the drug *in vivo*. Pharmacodynamic markers are of particular use in increasing the sensitivity of detection of drug effects, particularly when the drug is administered in low doses. Since even a small amount of a drug may be sufficient to activate multiple rounds of marker transcription or expression, the amplified marker may be in a quantity which is more readily detectable than the drug itself. Also, the marker may be more easily detected due to the nature of the marker itself; for example, using the methods described herein, antibodies may be employed in an immune-based detection system for a protein marker, or marker-specific radiolabeled probes may be used to detect a mRNA marker. Furthermore, the use of a pharmacodynamic marker may offer mechanism-based prediction of risk due to drug treatment beyond the range of possible direct observations. Examples of the use of pharmacodynamic markers in the art include: Matsuda *et al.* US 6,033,862; Hattis *et al.* (1991) *Env. Health Perspect.* 90: 229-238; Schentag (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S21-S24; and Nicolau (1999) *Am. J. Health-Syst. Pharm.* 56 Suppl. 3: S16-S20.

VI. Experimental Protocol for all OV markers and M352 - M360

A. Identification of markers

The markers of the present invention were identified by transcriptional
5 profiling using mRNA from 9 normal ovarian epithelia, 11 stage I/II ovarian cancer
tumors and 25 stage III/IV tumors. Clones having expression at least two-fold higher in
ovarian tumors as compared to their expression in non-ovarian tumor tissues in at least 4
tumor samples were selected to have their protein-encoding transcript sequences
determined.

10

B. Identification of Markers and Assembly of Their Sequences

Clones which displayed an increase in expression in ovarian tumor
samples over the corresponding average expression of non-tumor samples were used for
further study. Briefly, BLAST analysis, against both public and proprietary sequence
15 databases, of EST sequences known to be associated with each clone was performed,
either directly or in the context of automatically, high-stringency assembled contiguous
sequences. An identification of protein sequence corresponding to the clone was
accomplished by obtaining one of the following:

a) a direct match between the protein sequence and at least one EST
20 sequence in one of its 6 possible translations;

b) a direct match between the nucleotide sequence for the mRNA
corresponding to the protein sequence and at least one EST sequence;

c) a match between the protein sequence and a contiguous assembly
(contig) of the EST sequences with other available EST sequences in the databases in
25 one of its 6 possible translations; or

d) a match between the nucleotide sequence for the mRNA
corresponding to the protein sequence and a contiguous assembly of the EST sequences
with other available EST sequences in the databases in one of its 6 possible translations.

C. Identification of Markers Having Newly-Identified Nucleotide and Amino Acid Sequences.

The markers of Table 2 include newly-identified amino acid sequences.

5 These sequences were found to be novel based on one of the following criteria:

a) the protein sequence found within available public databases was incomplete or erroneous, leading to the construction of an additional completed/corrected protein sequence that is not found as such in the public domain;

b) based on nucleotide evidence, variants of the protein sequence were
10 additionally constructed that are not found as such in the public domain; or

c) the contig for the EST sequences did not match any known protein, so that a novel protein sequence was derived from an open reading frame of the contig.

15 VII. Experimental Protocol for M68, M103, M138, M185, M312, M327-M328, M400, M430-M480, M559, M571-M573, M575-M576, M578-M583, M585-594, and M604-M617

A. Identification of Markers and Assembly of Their Sequences

20 The markers of the present invention were identified by transcription profiling using mRNA from 67 ovarian tumors of various histotypes and stage and 96 non-ovarian tumor tissues including normal ovarian epithelium, benign conditions, other normal tissues, and other abnormal tissues. Clones having expression at least three-fold higher in at least 10% of ovarian tumors, as compared to their expression in non-ovarian
25 tumor tissue, were designated as ovarian cancer specific markers. These cDNA clones were selected to have their protein-encoding transcript sequences determined. Briefly, BLAST analysis, against both public and proprietary sequence databases, of EST sequences known to be associated with each clone was performed, either directly or in the context of automatically, high-stringency assembled contiguous sequences. An
30 identification of protein sequence corresponding to the clone was accomplished by obtaining one of the following:

a) a direct match between the protein sequence and at least one EST sequence in one of its 6 possible translations;

b) a direct match between the nucleotide sequence for the mRNA corresponding to the protein sequence and at least one EST sequence;

c) a match between the protein sequence and a contiguous assembly (contig) of the EST sequences with other available EST sequences in the databases in
5 one of its 6 possible translations; or

d) a match between the nucleotide sequence for the mRNA corresponding to the protein sequence and a contiguous assembly of the EST sequences with other available EST sequences in the databases in one of its 6 possible translations.

10 B. Identification of Markers Having Newly-Identified Amino Acid Sequences.

The markers of Table 2 include newly-identified amino acid sequences. These sequences were found to be novel based on one of the following criteria:

- a) the protein sequence found within available public databases was
15 incomplete or erroneous, leading to the construction of an additional completed/corrected protein sequence that is not found as such in the public domain;
- b) based on nucleotide evidence, variants of the protein sequence were additionally constructed that are not found as such in the public domain; or
- c) the contig for the EST sequences did not match any known protein, so
20 that a novel protein sequence was derived from an open reading frame of the contig.

VIII. Gene Expression Analysis

Total RNA from normal human tissue was obtained from commercial sources. The integrity of the RNA was verified by agarose gel electrophoresis and
25 ethidium bromide staining. Cell lines were purchased from ATCC and grown under the conditions recommended by ATCC. Total RNA from a number of various cell lines was prepared using commercial kits (Qiagen). First strand cDNA was prepared using oligo-dT primer and standard conditions. Each RNA preparation was treated with DNase I (Ambion) at 37°C for 1 hour.

30 Novel gene expression was measured by TaqMan[®] quantitative PCR (Perkin Elmer Applied Biosystems) in cDNA prepared from the following normal human tissues: heart, kidney, skeletal muscle, pancreas, skin, dorsal root ganglion,

breast, ovary, prostate, salivary glands, lung, colon, liver and lymph node. Figure 1 graphically represents the results of the TaqMan® expression study. The columns labelled A to V depict the expression level observed for OV88 in the following tissues:

- Column A: Heart, normal tissue
- 5 Column B: Heart, CHF tissue
- Column C: Kidney, normal tissue
- Column D: Skeletal muscle, normal tissue
- Column E: Pancreas, normal tissue
- Column F: Skin, normal tissue
- 10 Column G: Dorsal root, normal tissue
- Column H: Breast, normal tissue
- Column I: Breast, tumor tissue
- Column J: Ovary, normal tissue
- Column K: Ovary, tumor tissue
- 15 Column L: Prostate, normal tissue
- Column M: Prostate, tumor tissue
- Column N: Salivary glands, normal tissue
- Column O: Lung, normal tissue
- Column P: Lung, tumor tissue
- 20 Column Q: Lung, COPD tissue
- Column R: Colon, IBD tissue
- Column S: Liver, normal tissue
- Column T: Liver fibrosis
- Column U: Lymph node, normal tissue
- 25 Column V: Positive control

IX. Summary of the Data Provided in the Tables

Tables 1-3 list the markers of the present invention. In the Tables the markers are identified with a name ("Marker"), the name the gene is commonly known
 30 by, if applicable ("Gene Name"), the Sequence Listing identifier of the cDNA sequence of a nucleotide transcript encoded by or corresponding to the marker ("SEQ ID NO (nts)"), the Sequence Listing identifier of the amino acid sequence of a protein encoded

by the nucleotide transcript ("SEQ ID NO (AAs)"), and the location of the protein coding sequence within the cDNA sequence ("CDS").

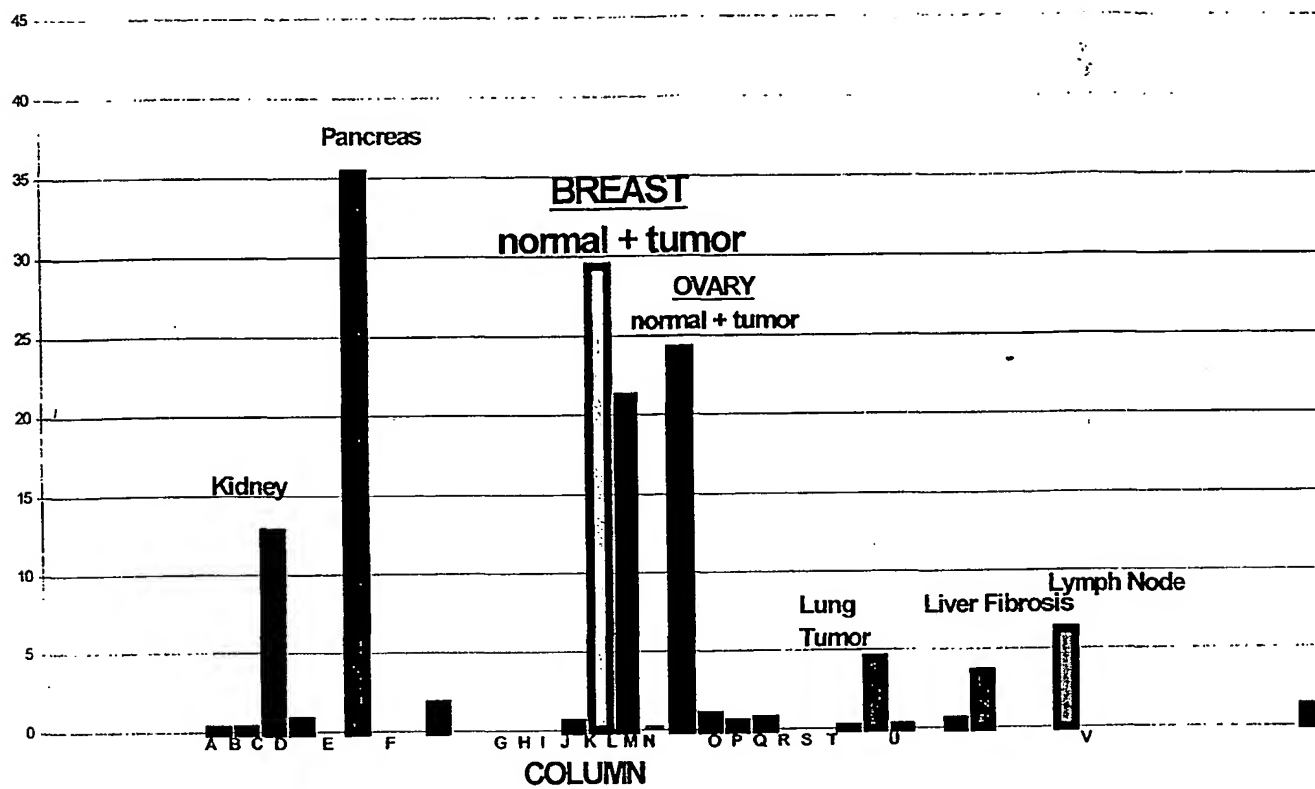
Table 1 lists all of the markers of the invention, which are over-expressed in ovarian cancer cells compared to normal (*i.e.*, non-cancerous) ovarian cells and
5 comprises markers listed in Tables 2 and 3. Table 2 lists newly-identified nucleotide and amino acid sequences useful as ovarian cancer markers. Table 3 lists newly-identified nucleotide sequences useful as ovarian cancer markers.

Other Embodiments

10 Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims:

What is claimed:

1. A method of assessing whether a patient is afflicted with ovarian cancer, the method comprising comparing:
 - 5 a) the level of expression of a marker in a patient sample, wherein the marker is selected from Table 1, and
 - b) the normal level of expression of the marker in a control non-ovarian cancer sample,wherein a significant increase in the level of expression of the marker in
10 the patient sample and the normal level is an indication that the patient is afflicted with ovarian cancer.

Figure 1

SEQUENCE LISTING

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Assessment, Prevention, and Therapy of Ovarian Cancer

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Glu	Leu	Glu	Arg	Tyr	Asn	Lys	Asn	Leu	Glu	Glu	Ala	Lys	Arg	Ile	Gly	275	280	285	
Ile	Lys	Lys	Ala	Ile	Thr	Ala	Asn	Ile	Ser	Ile	Gly	Ala	Ala	Phe	Leu	290	295	300	
Leu	Ile	Tyr	Ala	Ser	Tyr	Ala	Leu	Ala	Phe	Trp	Tyr	Gly	Thr	Thr	Leu	305	310	315	320
Val	Leu	Ser	Gly	Glu	Tyr	Ser	Ile	Gly	Gln	Val	Leu	Thr	Val	Phe	Ser	325	330	335	
Val	Leu	Ile	Gly	Ala	Phe	Ser	Val	Gly	Gln	Ala	Ser	Pro	Ser	Ile	Glu	340	345	350	
Ala	Phe	Ala	Asn	Ala	Arg	Gly	Ala	Ala	Tyr	Glu	Ile	Phe	Lys	Ile	Ile	355	360	365	
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Asp	Asn	Ile	Lys	Gly	Asn	Leu	Glu	Phe	Arg	Asn	Val	His	Phe	Ser	Tyr	385	390	395	400
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Gln	Ser	Gly	Gln	Thr	Val	Ala	Leu	Val	Gly	Asn	Ser	Gly	Cys	Gly	Lys	420	425	430	
Ser	Thr	Thr	Val	Gln	Leu	Met	Gln	Arg	Leu	Tyr	Asp	Pro	Thr	Glu	Gly	435	440	445	
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Met	Lys	Leu	Pro	His	Lys	Phe	Asp	Thr	Leu	Val	Gly	Glu	Arg	Gly	Ala	515	520	525	
Gln	Leu	Ser	Gly	Gly	Gln	Lys	Gln	Arg	Ile	Ala	Ile	Ala	Arg	Ala	Leu	530	535	540	
Val	Arg	Asn	Pro	Lys	Ile	Leu	Leu	Leu	Asp	Glu	Ala	Thr	Ser	Ala	Leu	545	550	555	560
Asp	Thr	Glu	Ser	Glu	Ala	Val	Val	Gln	Val	Ala	Leu	Asp	Lys	Ala	Arg	565	570	575	
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Asp	Ala	Ile	Glu	Gln	Phe	Met	Lys	Leu	Tyr	Glu	Glu	Lys	Thr	Gly	Asn		
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Ala	Trp	His	Ser	Lys	Asn	Phe	Thr	Lys	Tyr	Pro	Lys	Lys	Phe	Tyr	Pro		
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tctagtctct cctgtaagcc aaagaaatga acattccaag gagttggaag tgaagtctat 1380
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<210> 6

<211> 339

<212> PRT

<213> Homo sapiens

<400> 6

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Phe Asp Ala Glu Arg Asp Ala Leu Asn Ile Glu Thr Ala Ile Lys Thr
      35           40           45
Lys Gly Val Asp Glu Val Thr Ile Val Asn Ile Leu Thr Asn Arg Ser
      50           55           60
Asn Ala Gln Arg Gln Asp Ile Ala Phe Ala Tyr Gln Arg Arg Thr Lys
65           70           75           80
Lys Glu Leu Ala Ser Ala Leu Lys Ser Ala Leu Ser Gly His Leu Glu
      85           90           95
Thr Val Ile Leu Gly Leu Leu Lys Thr Pro Ala Gln Tyr Asp Ala Ser
      100          105          110
Glu Leu Lys Ala Ser Met Lys Gly Leu Gly Thr Asp Glu Asp Ser Leu
      115          120          125
Ile Glu Ile Ile Cys Ser Arg Thr Asn Gln Glu Leu Gln Glu Ile Asn
      130          135          140
Arg Val Tyr Lys Glu Met Tyr Lys Thr Asp Leu Glu Lys Asp Ile Ile
145          150          155          160
Ser Asp Thr Ser Gly Asp Phe Arg Lys Leu Met Val Ala Leu Ala Lys
      165          170          175
Gly Arg Arg Ala Glu Asp Gly Ser Val Ile Asp Tyr Glu Leu Ile Asp
      180          185          190
Gln Asp Ala Arg Asp Leu Tyr Asp Ala Gly Val Lys Arg Lys Gly Thr
      195          200          205
Asp Val Pro Lys Trp Ile Ser Ile Met Thr Glu Arg Ser Val Pro His
      210          215          220
Leu Gln Lys Val Phe Asp Arg Tyr Lys Ser Tyr Ser Pro Tyr Asp Met
225          230          235          240
Leu Glu Ser Ile Arg Lys Glu Val Lys Gly Asp Leu Glu Asn Ala Phe
      245          250          255
Leu Asn Leu Val Gln Cys Ile Gln Asn Lys Pro Leu Tyr Phe Ala Asp
      260          265          270
Arg Leu Tyr Asp Ser Met Lys Gly Lys Gly Thr Arg Asp Lys Val Leu
      275          280          285
Ile Arg Ile Met Val Ser Arg Ser Glu Val Asp Met Leu Lys Ile Arg
      290          295          300
Ser Glu Phe Lys Arg Lys Tyr Gly Lys Ser Leu Tyr Tyr Tyr Ile Gln
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Gly Asp Asp

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 <211> 1362
 <212> DNA
 <213> Homo sapiens

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<210> 8
 <211> 339
 <212> PRT
 <213> Homo sapiens

<400> 8
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 Phe Asp Ala Glu Arg Asp Ala Leu Asn Ile Glu Thr Ala Ile Lys Thr
 35 40 45
 Lys Gly Val Asp Glu Val Thr Ile Val Asn Ile Leu Thr Asn Arg Ser
 50 55 60
 Asn Ala Gln Arg Gln Asp Ile Ala Phe Ala Tyr Gln Arg Arg Thr Lys
 65 70 75 80
 Lys Glu Leu Ala Ser Ala Leu Lys Ser Ala Leu Ser Gly His Leu Glu
 85 90 95
 Thr Val Ile Leu Gly Leu Leu Lys Thr Pro Ala Gln Tyr Asp Ala Ser
 100 105 110
 Glu Leu Lys Ala Ser Met Lys Gly Leu Gly Thr Asp Glu Asp Ser Leu
 115 120 125
 Ile Glu Ile Ile Cys Ser Arg Thr Asn Gln Glu Leu Gln Glu Ile Asn
 130 135 140
 Arg Val Tyr Lys Glu Met Tyr Lys Thr Asp Leu Glu Lys Asp Ile Ile
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 165 170 175

Gly Arg Arg Ala Glu Asp Gly Ser Val Ile Asp Tyr Glu Leu Ile Asp
 180 185 190
 Gln Asp Ala Arg Asp Leu Tyr Asp Ala Gly Val Lys Arg Lys Gly Thr
 195 200 205
 Asp Val Pro Lys Trp Ile Ser Ile Met Thr Glu Arg Ser Val Pro His
 210 215 220
 Leu Gln Lys Val Phe Asp Arg Tyr Lys Ser Tyr Ser Pro Tyr Asp Met
 225 230 235 240
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 245 250 255
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 260 265 270
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 275 280 285
 Ile Arg Ile Met Val Ser Arg Ser Glu Val Asp Met Leu Lys Ile Arg
 290 295 300
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 <211> 1982
 <212> DNA
 <213> Homo sapiens

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<210> 10
 <211> 321
 <212> PRT
 <213> Homo sapiens

<400> 10

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			20					25					30		
Gly	Thr	Asp	Glu	Asp	Ala	Ile	Ile	Ser	Val	Leu	Ala	Tyr	Arg	Asn	Thr
		35				40						45			
Ala	Gln	Arg	Gln	Glu	Ile	Arg	Thr	Ala	Tyr	Lys	Ser	Thr	Ile	Gly	Arg
	50				55						60				
Asp	Leu	Ile	Asp	Asp	Leu	Lys	Ser	Glu	Leu	Ser	Gly	Asn	Phe	Glu	Gln
65					70					75				80	
Val	Ile	Val	Gly	Met	Thr	Pro	Thr	Val	Leu	Tyr	Asp	Val	Gln	Glu	
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Glu	Ile	Leu	Ala	Ser	Arg	Thr	Pro	Glu	Glu	Ile	Arg	Arg	Ile	Ser	Gln
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Ala	Gln	Asp	Leu	Tyr	Glu	Ala	Gly	Glu	Lys	Lys	Trp	Gly	Thr	Asp	Glu
		180					185						190		
Val	Lys	Phe	Leu	Thr	Val	Leu	Cys	Ser	Arg	Asn	Arg	Asn	His	Leu	Leu
	195					200					205				
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	210					215					220				
Ser	Ile	Lys	Ser	Glu	Thr	Ser	Gly	Ser	Phe	Glu	Asp	Ala	Leu	Leu	Ala
225					230					235				240	
Ile	Val	Lys	Cys	Met	Arg	Asn	Lys	Ser	Ala	Tyr	Phe	Ala	Glu	Lys	Leu
			245					250						255	
Tyr	Lys	Ser	Met	Lys	Gly	Leu	Gly	Thr	Asp	Asp	Asn	Thr	Leu	Ile	Arg
		260					265						270		
Val	Met	Val	Ser	Arg	Ala	Glu	Ile	Asp	Met	Leu	Asp	Ile	Arg	Ala	His
		275					280					285			
Phe	Lys	Arg	Leu	Tyr	Gly	Lys	Ser	Leu	Tyr	Ser	Phe	Ile	Lys	Gly	Asp
	290				295						300				
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<210> 11

<211> 1316
 <212> DNA
 <213> Homo sapiens

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 <211> 265
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Phe Gly Leu Ala Ile Gly Thr Leu Ala Gln Ala Leu Gly Pro Val Ser
 50 55 60
 Gly Gly His Ile Asn Pro Ala Ile Thr Leu Ala Leu Leu Val Gly Asn
 65 70 75 80
 Gln Ile Ser Leu Leu Arg Ala Phe Phe Tyr Val Ala Ala Gln Leu Val
 85 90 95
 Gly Ala Ile Ala Gly Ala Gly Ile Leu Tyr Gly Val Ala Pro Leu Asn
 100 105 110
 Ala Arg Gly Asn Leu Ala Val Asn Ala Leu Asn Asn Asn Thr Thr Gln
 115 120 125
 Gly Gln Ala Met Val Val Glu Leu Ile Leu Thr Phe Gln Leu Ala Leu
 130 135 140
 Cys Ile Phe Ala Ser Thr Asp Ser Arg Arg Thr Ser Pro Val Gly Ser
 145 150 155 160
 Pro Ala Leu Ser Ile Gly Leu Ser Val Thr Leu Gly His Leu Val Gly
 165 170 175
 Ile Tyr Phe Thr Gly Cys Ser Met Asn Pro Ala Arg Ser Phe Gly Pro
 180 185 190

Ala Val Val Met Asn Arg Phe Ser Pro Ala His Trp Val Phe Trp Val
 195 200 205
 Gly Pro Ile Val Gly Ala Val Leu Ala Ala Ile Leu Tyr Phe Tyr Leu
 210 215 220
 Leu Phe Pro Asn Ser Leu Ser Leu Ser Glu Arg Val Ala Ile Ile Lys
 225 230 235 240
 Gly Thr Tyr Glu Pro Asp Glu Asp Trp Glu Glu Gln Arg Glu Glu Arg
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 <211> 1653
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 <213> Homo sapiens

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 <211> 464
 <212> PRT
 <213> Homo sapiens

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	50					55					60				
Tyr	Val	Glu	Asn	Asp	Tyr	Thr	Ile	Val	Tyr	Phe	His	Tyr	Gly	Leu	Asn
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Ser	Arg	Asn	Lys	Pro	Ser	Leu	Gly	Trp	Leu	Gln	Ser	Ala	Tyr	Lys	Glu
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Phe	Asp	Arg	Lys	Asp	Gly	Asp	Leu	Thr	Met	Trp	Pro	Arg	Leu	Val	Ser
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Thr	Ser	Phe	Ile	Lys	Val	Leu	Trp	Asn	Ile	Leu	Lys	Pro	Leu	Ile	Ser
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	210					215					220				
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Arg	Thr	Glu	Gly	Leu	Phe	Arg	Arg	Ser	Ala	Ser	Val	Gln	Thr	Val	Arg
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Glu	Ile	Gln	Arg	Leu	Tyr	Asn	Gln	Gly	Lys	Pro	Val	Asn	Phe	Asp	Asp
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<211> 2043

<212> DNA

<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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35          40          45
Gly Val Ile Ala Val Phe Gln Arg Lys Gly Leu Pro Asp Gln Glu Leu
50          55          60
Phe Ser Leu Asn Glu Gly Val Arg Gln Leu Leu Lys Thr Glu Leu Gly
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85          90          95

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Gln	Gln	Phe	Gly	Val	Ser	Leu	Gln	Tyr	Leu	Lys	Asp	Lys	Asn	Gln	Gly		
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Glu	Leu	Ile	Pro	Pro	Val	Leu	Arg	Phe	Thr	Val	Thr	Tyr	Leu	Arg	Glu		
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Thr	Val	Arg	Glu	Ile	Gln	Arg	Leu	Tyr	Asn	Gln	Gly	Lys	Pro	Val	Asn		
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Lys	Leu	Glu	Asp 165	Ala	Leu	Ala	Arg	Ala 170	His	Ala	Arg	Val	Pro 175	Pro	Ala
Ile	Val	Gln	Met 180	Leu	Leu	Val	Leu 185	Gln	Gly	Val	His	Glu	Ser 190	Arg	Gly
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Thr 225	His	Ser	Cys	Ile 230	Leu	Glu	Leu	Gln	Arg 235	Asp	Lys	Ala	Ala	Ala 240	Ala
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Lys	Leu	Lys	Arg	Ser	Ser	His	Leu	Ser	Leu	Pro	Lys	Tyr	Trp	Asp	Tyr	370	375	380
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Ser	Asn	Leu	Ala	Cys	Val	Phe	Gly	Leu	Asn	Leu	Ile	Trp	Pro	Ser	Gln	625	630	635
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Gly	Glu	His	Gly	Leu	Ala	Pro	Trp	Glu	Gln	Gly	Ser	Arg	Ala	Ala	Pro	675	680	685
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Thr	Leu	Pro	Pro	Ser	Pro	Leu	Met	Ala	Ala	Arg	Arg	Arg	Leu	Xaa	Cys	705	710	715
Cys	Glu	His	Ser	Val	Tyr	Phe	Glu	Leu	Pro	Pro	Thr	Pro	Val	Cys	Ala	725	730	735
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Lys	Thr	Pro	Pro	Pro	Arg	Pro	Pro	Leu	Pro	Thr	Gln	Gln	Phe	Gly	Val
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 <213> Homo sapiens

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<210> 21

<211> 390

<212> PRT

<213> Homo sapiens

<400> 21

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 50          55          60
Leu Tyr Val Val His Pro Thr Ser Phe Ile Lys Val Leu Trp Asn Ile
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Leu Lys Pro Leu Ile Ser His Lys Phe Gly Lys Lys Val Ile Tyr Phe
 85          90          95
Asn Tyr Leu Ser Glu Leu His Glu His Leu Lys Tyr Asp Gln Leu Val
100          105          110
Ile Pro Pro Glu Val Leu Arg Tyr Asp Glu Lys Leu Gln Ser Leu His
115          120          125
Glu Gly Arg Thr Pro Pro Pro Thr Lys Thr Pro Pro Pro Arg Pro Pro
130          135          140
Leu Pro Thr Gln Gln Phe Gly Val Ser Leu Gln Tyr Leu Lys Asp Lys
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Asn Gln Gly Glu Leu Ile Pro Pro Val Leu Arg Phe Thr Val Thr Tyr
165          170          175
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180          185          190
Ser Val Gln Thr Val Arg Glu Ile Gln Arg Leu Tyr Asn Gln Gly Lys
195          200          205
Pro Val Asn Phe Asp Asp Tyr Gly Asp Ile His Ile Pro Ala Val Ile
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Leu Lys Thr Phe Leu Arg Glu Leu Pro Gln Pro Leu Leu Thr Phe Gln
225          230          235          240
Ala Tyr Glu Gln Ile Leu Gly Ile Thr Cys Val Glu Ser Ser Leu Arg
245          250          255
Val Thr Gly Cys Arg Gln Ile Leu Arg Ser Leu Pro Glu His Asn Tyr
260          265          270
Val Val Leu Arg Tyr Leu Met Gly Phe Leu His Ala Val Ser Arg Glu
275          280          285
Ser Ile Phe Asn Lys Met Asn Ser Ser Asn Leu Ala Cys Val Phe Gly
290          295          300
Leu Asn Leu Ile Trp Pro Ser Gln Gly Val Ser Ser Leu Ser Ala Leu
305          310          315          320
Val Pro Leu Asn Met Phe Thr Glu Leu Leu Ile Glu Tyr Tyr Glu Lys
325          330          335
Ile Phe Ser Thr Pro Glu Ala Pro Gly Glu His Gly Leu Ala Pro Trp
340          345          350
Glu Gln Gly Ser Arg Ala Ala Pro Leu Gln Glu Ala Val Pro Arg Thr
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Gln Ala Thr Gly Leu Thr Lys Pro Thr Leu Pro Pro Ser Pro Leu Met

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<211> 2019
<212> DNA
<213> Homo sapiens

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<210> 23
<211> 633
<212> PRT
<213> Homo sapiens

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Gln Gln Arg Arg Ala Cys Ala Asn Ala Thr Trp Asn Ser Ile His Asn
35 40 45

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Phe	Ser	Leu	Asn	Glu	Gly	Val	Arg	Gln	Leu	Leu	Lys	Thr	Glu	Leu	Gly	65	70	75
Ser	Phe	Phe	Thr	Glu	Tyr	Leu	Gln	Asn	Gln	Leu	Leu	Thr	Lys	Gly	Met	85	90	95
Val	Ile	Leu	Arg	Asp	Lys	Ile	Arg	Phe	Tyr	Glu	Gly	Gln	Lys	Leu	Leu	100	105	110
Asp	Ser	Leu	Ala	Glu	Thr	Trp	Asp	Phe	Phe	Phe	Ser	Asp	Val	Leu	Pro	115	120	125
Met	Leu	Gln	Ala	Ile	Phe	Tyr	Pro	Val	Gln	Gly	Lys	Glu	Pro	Ser	Val	130	135	140
Arg	Gln	Leu	Ala	Leu	Leu	His	Phe	Arg	Asn	Ala	Ile	Thr	Leu	Ser	Val	145	150	155
Lys	Leu	Glu	Asp	Ala	Leu	Ala	Arg	Ala	His	Ala	Arg	Val	Pro	Pro	Ala	165	170	175
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Val	Thr	Glu	Asp	Tyr	Leu	Arg	Leu	Glu	Thr	Leu	Val	Gln	Lys	Val	Val	195	200	205
Ser	Pro	Tyr	Leu	Gly	Thr	Tyr	Gly	Leu	His	Ser	Ser	Glu	Gly	Pro	Phe	210	215	220
Thr	His	Ser	Cys	Ile	Leu	Glu	Leu	Gln	Arg	Asp	Lys	Ala	Ala	Ala	Ala	225	230	235
Ala	Val	Leu	Gly	Ala	Val	Arg	Lys	Arg	Pro	Ser	Val	Val	Pro	Met	Ala	245	250	255
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Arg	Lys	Asp	Gly	Asp	Leu	Thr	Met	Trp	Pro	Arg	Leu	Val	Ser	Asn	Ser	355	360	365
Lys	Leu	Lys	Arg	Ser	Ser	His	Leu	Ser	Leu	Pro	Lys	Tyr	Trp	Asp	Tyr	370	375	380
Arg	Tyr	Lys	Lys	Asn	Leu	Lys	Ala	Leu	Tyr	Val	Val	His	Pro	Thr	Ser	385	390	395
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Phe	Gly	Lys	Lys	Val	Ile	Tyr	Phe	Asn	Tyr	Leu	Ser	Glu	Leu	His	Glu	420	425	430
His	Leu	Lys	Tyr	Asp	Gln	Leu	Val	Ile	Pro	Pro	Glu	Val	Leu	Arg	Tyr	435	440	445
Asp	Glu	Lys	Leu	Gln	Ser	Leu	His	Glu	Gly	Arg	Thr	Pro	Pro	Pro	Thr	450	455	460
Lys	Thr	Pro	Pro	Pro	Arg	Pro	Pro	Leu	Pro	Thr	Gln	Gln	Phe	Gly	Val	465	470	475
Ser	Leu	Gln	Tyr	Leu	Lys	Asp	Lys	Asn	Gln	Gly	Glu	Leu	Ile	Pro	Pro	485	490	495
Val	Leu	Arg	Phe	Thr	Val	Thr	Tyr	Leu	Arg	Glu	Lys	Gly	Leu	Pro	Glu	500	505	510

His Asn Tyr Val Val Leu Arg Tyr Leu Met Gly Phe Leu His Ala Val
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 Ser Arg Glu Ser Ile Phe Asn Lys Met Asn Ser Ser Asn Leu Ala Cys
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 Val Phe Gly Leu Asn Leu Ile Trp Pro Ser Gln Gly Val Ser Ser Leu
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 Ser Ala Leu Val Pro Leu Asn Met Phe Thr Glu Leu Leu Ile Glu Tyr
 565 570 575
 Tyr Glu Lys Ile Phe Ser Thr Pro Glu Ala Pro Gly Glu His Gly Leu
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 Ala Pro Trp Glu Gln Gly Ser Arg Ala Ala Pro Leu Gln Glu Ala Val
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 <212> PRT
 <213> Homo sapiens

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<210> 27

<211> 461

<212> PRT

<213> Homo sapiens

<400> 27

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Gln Gln Arg Arg Ala Cys Ala Asn Ala Thr Trp Asn Ser Ile His Asn
      35           40           45
Gly Val Ile Ala Val Phe Gln Arg Lys Gly Leu Pro Asp Gln Glu Leu
      50           55           60
Phe Ser Leu Asn Glu Gly Val Arg Gln Leu Leu Lys Thr Glu Leu Gly
      65           70           75           80
Ser Phe Phe Thr Glu Tyr Leu Gln Asn Gln Leu Leu Thr Lys Gly Met
      85           90           95
Val Ile Leu Arg Asp Lys Ile Arg Phe Tyr Glu Gly Gln Lys Leu Leu
      100          105          110
Asp Ser Leu Ala Glu Thr Trp Asp Phe Phe Phe Ser Asp Val Leu Pro
      115          120          125
Met Leu Gln Ala Ile Phe Tyr Pro Val Gln Gly Lys Glu Pro Ser Val
      130          135          140
Arg Gln Leu Ala Leu Leu His Phe Arg Asn Ala Ile Thr Leu Ser Val
      145          150          155          160
Lys Leu Glu Asp Ala Leu Ala Arg Ala His Ala Arg Val Pro Pro Ala
      165          170          175
Ile Val Gln Met Leu Leu Val Leu Gln Gly Val His Glu Ser Arg Gly
      180          185          190
Val Thr Glu Asp Tyr Leu Arg Leu Glu Thr Leu Val Gln Lys Val Val
      195          200          205

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				245					250					255	
Gly	Gln	Asp	Pro	Ala	Leu	Ser	Thr	Ser	His	Pro	Phe	Tyr	Asp	Val	Ala
			260					265					270		
Arg	His	Gly	Ile	Leu	Gln	Val	Ala	Gly	Asp	Asp	Arg	Phe	Gly	Arg	Arg
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Val	Val	Thr	Phe	Ser	Cys	Cys	Arg	Met	Pro	Pro	Ser	His	Glu	Leu	Asp
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His	Gln	Arg	Leu	Leu	Glu	Tyr	Lys	Lys	Asn	Leu	Lys	Ala	Leu	Tyr	Val
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Val	His	Pro	Thr	Ser	Phe	Ile	Lys	Val	Leu	Trp	Asn	Ile	Leu	Lys	Pro
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Ser	Glu	Leu	His	Glu	His	Leu	Lys	Tyr	Asp	Gln	Leu	Val	Ile	Pro	Pro
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	370					375					380				
Thr	Pro	Pro	Pro	Thr	Lys	Thr	Pro	Pro	Pro	Arg	Pro	Pro	Leu	Pro	Thr
385					390					395					400
Gln	Gln	Phe	Gly	Val	Ser	Leu	Gln	Tyr	Leu	Lys	Asp	Lys	Asn	Gln	Gly
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Glu	Leu	Ile	Pro	Pro	Val	Leu	Arg	Phe	Thr	Val	Thr	Tyr	Leu	Arg	Glu
			420					425					430		
Lys	Ala	Ser	Gln	Ser	Thr	Thr	Thr	Ser	Ser	Ser	Ala	Thr	Ser	Trp	Ala
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Ser	Cys	Met	Arg	Cys	Pro	Gly	Arg	Ala	Ser	Ser	Thr	Lys			
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<210> 28
 <211> 1176
 <212> DNA
 <213> Homo sapiens

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<212> PRT

<213> Homo sapiens

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<212> DNA
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Asp Ala Glu Ser Tyr Thr Phe Thr Val Pro Arg Arg His Leu Glu Arg
 35          40          45
Gly Arg Val Leu Gly Arg Val Asn Phe Glu Asp Cys Thr Gly Arg Gln
 50          55          60
Arg Thr Ala Tyr Phe Ser Leu Asp Thr Arg Phe Lys Val Gly Thr Asp
 65          70          75          80
Gly Val Ile Thr Val Lys Arg Pro Leu Arg Phe His Asn Pro Gln Ile
 85          90          95
His Phe Leu Val Tyr Ala Trp Asp Ser Thr Tyr Arg Lys Phe Ser Thr
 100          105          110
Lys Val Thr Leu Asn Thr Val Gly His His His Arg Pro Pro Pro His
 115          120          125
Gln Ala Ser Val Ser Gly Ile Gln Ala Glu Leu Leu Thr Phe Pro Asn
 130          135          140
Ser Ser Pro Gly Leu Arg Arg Gln Lys Arg Asp Trp Val Ile Pro Pro
 145          150          155          160
Ile Ser Cys Pro Glu Asn Glu Lys Gly Pro Phe Pro Lys Asn Leu Val
 165          170          175
Gln Ile Lys Ser Asn Lys Asp Lys Glu Gly Lys Val Phe Tyr Ser Ile
 180          185          190
Thr Gly Gln Gly Ala Asp Thr Pro Pro Val Gly Val Phe Ile Ile Glu
 195          200          205
Arg Glu Thr Gly Trp Leu Lys Val Thr Glu Pro Leu Asp Arg Glu Arg
 210          215          220
Ile Ala Thr Tyr Thr Leu Phe Ser His Ala Val Ser Ser Asn Gly Asn
 225          230          235          240
Ala Val Glu Asp Pro Met Glu Ile Leu Ile Thr Val Thr Asp Gln Asn
 245          250          255
Asp Asn Lys Pro Glu Phe Thr Gln Glu Val Phe Lys Gly Ser Val Met
 260          265          270
Glu Gly Ala Leu Pro Gly Thr Ser Val Met Glu Val Thr Ala Thr Asp
 275          280          285
Ala Asp Asp Asp Val Asn Thr Tyr Asn Ala Ala Ile Ala Tyr Thr Ile
 290          295          300
Leu Ser Gln Asp Pro Glu Leu Pro Asp Lys Asn Met Phe Thr Ile Asn
 305          310          315          320
Arg Asn Thr Gly Val Ile Ser Val Val Thr Thr Gly Leu Asp Arg Glu
 325          330          335
Ser Phe Pro Thr Tyr Thr Leu Val Val Gln Ala Ala Asp Leu Gln Gly
 340          345          350
Glu Gly Leu Ser Thr Thr Ala Thr Ala Val Ile Thr Val Thr Asp Thr
 355          360          365
Asn Asp Asn Pro Pro Ile Phe Asn Pro Thr Thr Tyr Lys Gly Gln Val
 370          375          380
Pro Glu Asn Glu Ala Asn Val Val Ile Thr Thr Leu Lys Val Thr Asp
 385          390          395          400
Ala Asp Ala Pro Asn Thr Pro Ala Trp Glu Ala Val Tyr Thr Ile Leu
 405          410          415
Asn Asp Asp Gly Gly Gln Phe Val Val Thr Thr Asn Pro Val Asn Asn
 420          425          430
Asp Gly Ile Leu Lys Thr Ala Lys Gly Leu Asp Phe Glu Ala Lys Gln

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Leu	Gln	Ile	Pro	Ala	Ile	Leu	Gly	Ile	Leu	Gly	Gly	Ile	Leu	Ala	Leu	
705					710					715					720	
Leu	Ile	Leu	Ile	Leu	Leu	Leu	Leu	Leu	Phe	Leu	Arg	Arg	Arg	Ala	Val	
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Tyr	Tyr	Tyr	Asp	Glu	Glu	Gly	Gly	Glu	Glu	Asp	Gln	Asp	Phe	Asp		
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Ala	Ala	Asp	Thr	Asp	Pro	Thr	Ala	Pro	Pro	Tyr	Asp	Ser	Leu	Leu	Val	
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Phe	Asp	Tyr	Glu	Gly	Ser	Gly	Ser	Glu	Ala	Ala	Ser	Leu	Ser	Ser	Leu	
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Asn	Ser	Ser	Glu	Ser	Asp	Lys	Asp	Gln	Asp	Tyr	Asp	Tyr	Leu	Asn	Glu	
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<210> 38
 <211> 4521
 <212> DNA
 <213> Homo sapiens

<400> 38

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<210> 39

<211> 790

<212> PRT

<213> Homo sapiens

<400> 39

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20           25           30
Ala Lys Lys Arg Ala Leu Glu Leu Ser Gly Asn Ser Lys Asn Glu Leu
35           40           45
Asn Arg Ser Lys Arg Ser Trp Met Trp Asn Gln Phe Phe Leu Leu Glu
50           55           60
Glu Tyr Thr Gly Ser Asp Tyr Gln Tyr Val Gly Lys Leu His Ser Asp
65           70           75           80
Gln Asp Arg Gly Asp Gly Ser Leu Lys Tyr Ile Leu Ser Gly Asp Gly
85           90           95
Ala Gly Asp Leu Phe Ile Ile Asn Glu Asn Thr Gly Asp Ile Gln Ala
100          105          110
Thr Lys Arg Leu Asp Arg Glu Glu Lys Pro Val Tyr Ile Leu Arg Ala
115          120          125
Gln Ala Ile Asn Arg Arg Thr Gly Arg Pro Val Glu Pro Glu Ser Glu
130          135          140
Phe Ile Ile Lys Ile His Asp Ile Asn Asp Asn Glu Pro Ile Phe Thr
145          150          155          160
Lys Glu Val Tyr Thr Ala Thr Val Pro Glu Met Ser Asp Val Gly Thr
165          170          175
Phe Val Val Gln Val Thr Ala Thr Asp Ala Asp Asp Pro Thr Tyr Gly
180          185          190
Asn Ser Ala Lys Val Val Tyr Ser Ile Leu Gln Gly Gln Pro Tyr Phe
195          200          205

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Ser	Val	Glu	Ser	Glu	Thr	Gly	Ile	Ile	Lys	Thr	Ala	Leu	Leu	Asn	Met
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Asp	Arg	Glu	Asn	Arg	Glu	Gln	Tyr	Gln	Val	Val	Ile	Gln	Ala	Lys	Asp
225					230					235					240
Met	Gly	Gly	Gln	Met	Gly	Gly	Leu	Ser	Gly	Thr	Thr	Thr	Val	Asn	Ile
				245					250					255	
Thr	Leu	Thr	Asp	Val	Asn	Asp	Asn	Pro	Pro	Arg	Phe	Pro	Gln	Ser	Thr
			260					265					270		
Tyr	Gln	Phe	Lys	Thr	Pro	Glu	Ser	Ser	Pro	Pro	Gly	Thr	Pro	Ile	Gly
		275					280					285			
Arg	Ile	Lys	Ala	Ser	Asp	Ala	Asp	Val	Gly	Glu	Asn	Ala	Glu	Ile	Glu
	290					295					300				
Tyr	Ser	Ile	Thr	Asp	Gly	Glu	Gly	Leu	Asp	Met	Phe	Asp	Val	Ile	Thr
305					310					315					320
Asp	Gln	Glu	Thr	Gln	Glu	Gly	Ile	Ile	Thr	Val	Lys	Lys	Leu	Leu	Asp
				325					330					335	
Phe	Glu	Lys	Lys	Lys	Val	Tyr	Thr	Leu	Lys	Val	Glu	Ala	Ser	Asn	Pro
		340						345					350		
Tyr	Val	Glu	Pro	Arg	Phe	Leu	Tyr	Leu	Gly	Pro	Phe	Lys	Asp	Ser	Ala
	355						360					365			
Thr	Val	Arg	Ile	Val	Val	Glu	Asp	Val	Asp	Glu	Pro	Pro	Val	Phe	Ser
	370					375					380				
Lys	Leu	Ala	Tyr	Ile	Leu	Gln	Ile	Arg	Glu	Asp	Ala	Gln	Ile	Asn	Thr
385					390					395					400
Thr	Ile	Gly	Ser	Val	Thr	Ala	Gln	Asp	Pro	Asp	Ala	Ala	Arg	Asn	Pro
			405						410					415	
Val	Lys	Tyr	Ser	Val	Asp	Arg	His	Thr	Asp	Met	Asp	Arg	Ile	Phe	Asn
		420						425					430		
Ile	Asp	Ser	Gly	Asn	Gly	Ser	Ile	Phe	Thr	Ser	Lys	Leu	Leu	Asp	Arg
	435						440					445			
Glu	Thr	Leu	Leu	Trp	His	Asn	Ile	Thr	Val	Ile	Ala	Thr	Glu	Ile	Asn
	450					455					460				
Asn	Pro	Lys	Gln	Ser	Ser	Arg	Val	Pro	Leu	Tyr	Ile	Lys	Val	Leu	Asp
465					470					475					480
Val	Asn	Asp	Asn	Ala	Pro	Glu	Phe	Ala	Glu	Phe	Tyr	Glu	Thr	Phe	Val
			485						490					495	
Cys	Glu	Lys	Ala	Lys	Ala	Asp	Gln	Leu	Ile	Gln	Thr	Leu	His	Ala	Val
		500						505					510		
Asp	Lys	Asp	Asp	Pro	Tyr	Ser	Gly	His	Gln	Phe	Ser	Phe	Ser	Leu	Ala
	515						520					525			
Pro	Glu	Ala	Ala	Ser	Gly	Ser	Asn	Phe	Thr	Ile	Gln	Asp	Asn	Lys	Asp
	530					535					540				
Asn	Thr	Ala	Gly	Ile	Leu	Thr	Arg	Lys	Asn	Gly	Tyr	Asn	Arg	His	Glu
545					550					555					560
Met	Ser	Thr	Tyr	Leu	Leu	Pro	Val	Val	Ile	Ser	Asp	Asn	Asp	Tyr	Pro
				565					570					575	
Val	Gln	Ser	Ser	Thr	Gly	Thr	Val	Thr	Val	Arg	Val	Cys	Ala	Cys	Asp
			580					585					590		
His	His	Gly	Asn	Met	Gln	Ser	Cys	His	Ala	Glu	Ala	Leu	Ile	His	Pro
	595						600					605			
Thr	Gly	Leu	Ser	Thr	Gly	Ala	Leu	Val	Ala	Ile	Leu	Leu	Cys	Ile	Val
	610					615					620				
Ile	Leu	Leu	Val	Thr	Val	Val	Leu	Phe	Ala	Ala	Leu	Arg	Arg	Gln	Arg
625					630					635					640
Lys	Lys	Glu	Pro	Leu	Ile	Ile	Ser	Lys	Glu	Asp	Ile	Arg	Asp	Asn	Ile
			645						650					655	
Val	Ser	Tyr	Asn	Asp	Glu	Gly	Gly	Gly	Glu	Glu	Asp	Thr	Gln	Ala	Phe
			660					665					670		

Asp Ile Gly Thr Leu Arg Asn Pro Glu Ala Ile Glu Asp Asn Lys Leu
 675 680 685
 Arg Arg Asp Ile Val Pro Glu Ala Leu Phe Leu Pro Arg Arg Thr Pro
 690 695 700
 Thr Ala Arg Asp Asn Thr Asp Val Arg Asp Phe Ile Asn Gln Arg Leu
 705 710 715 720
 Lys Glu Asn Asp Thr Asp Pro Thr Ala Pro Pro Tyr Asp Ser Leu Ala
 725 730 735
 Thr Tyr Ala Tyr Glu Gly Thr Gly Ser Val Ala Asp Ser Leu Ser Ser
 740 745 750
 Leu Glu Ser Val Thr Thr Asp Ala Asp Gln Asp Tyr Asp Tyr Leu Ser
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 Asp Trp Gly Pro Arg Phe Lys Lys Leu Ala Asp Met Tyr Gly Gly Val
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 785 790

<210> 40
 <211> 987
 <212> DNA
 <213> Homo sapiens

<400> 40
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<210> 41
 <211> 156
 <212> PRT
 <213> Homo sapiens

<400> 41
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 Glu Ala Gly Ala Leu Pro Asn Ala Pro Asn Ser Tyr Gly Arg Arg Pro
 35 40 45
 Ile Gln Val Met Met Met Gly Ser Ala Arg Val Ala Glu Leu Leu Leu
 50 55 60
 Leu His Gly Ala Glu Pro Asn Cys Ala Asp Pro Ala Thr Leu Thr Arg
 65 70 75 80

Pro	Val	His	Asp	Ala	Ala	Arg	Glu	Gly	Phe	Leu	Asp	Thr	Leu	Val	Val
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Leu	His	Arg	Ala	Gly	Ala	Arg	Leu	Asp	Val	Arg	Asp	Ala	Trp	Gly	Arg
			100					105					110		
Leu	Pro	Val	Asp	Leu	Ala	Glu	Glu	Leu	Gly	His	Arg	Asp	Val	Ala	Arg
			115					120					125		
Tyr	Leu	Arg	Ala	Ala	Ala	Gly	Gly	Thr	Arg	Gly	Ser	Asn	His	Ala	Arg
			130					135					140		
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<210> 42
 <211> 5142
 <212> DNA
 <213> Homo sapiens

<400> 42

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<210> 43

<211> 1203

<212> PRT

<213> Homo sapiens

<400> 43

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545					550					555					
Leu	Glu	Glu	Thr	Ser	Glu	Glu	Thr	Gly	His	Trp	Gln	Ser	Met	Phe	Gln
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Trp	Ala	Ser	Glu	Ala	Glu	Lys	Thr	Ser	Gly	Gly	Leu	Ser	Arg	Leu	Gln
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Asp	Glu	Ile	Gln	Arg	Leu	Arg	Gln	Ala	Leu	Gln	Ala	Ser	Gln	Ala	Glu
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Arg	Asp	Thr	Ala	Arg	Leu	Asp	Lys	Glu	Leu	Leu	Ala	Gln	Arg	Leu	Gln
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Gly	Leu	Glu	Gln	Glu	Ala	Glu	Asn	Lys	Lys	Arg	Ser	Gln	Asp	Asp	Arg
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Arg Gln Asn Lys Asp Leu Lys Thr Arg Leu Ala Ser Ser Glu Gly Phe					
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Gln Lys Pro Ser Ala Ser Leu Ser Gln Leu Glu Ser Gln Asn Gln Leu					
	1045	1050		1055	
Leu Gln Glu Arg Leu Gln Ala Glu Glu Arg Glu Lys Thr Val Leu Gln					
	1060	1065		1070	
Ser Thr Asn Arg Lys Leu Glu Arg Lys Val Lys Glu Leu Ser Ile Gln					
	1075	1080		1085	
Ile Glu Asp Glu Arg Gln His Val Asn Asp Gln Lys Asp Gln Leu Ser					
	1090	1095		1100	
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Ile Glu Arg Leu Asp Gly Leu Arg Lys Lys Ala Gln Arg Glu Val Glu					
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Glu Gln His Glu Val Asn Glu Gln Leu Gln Ala Arg Ile Lys Ser Leu					
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Glu Lys Asp Ser Trp Arg Lys Ala Ser Arg Ser Ala Ala Glu Ser Ala					
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Leu Lys Asn Glu Gly Leu Ser Ser Asp Glu Glu Phe Asp Ser Val Tyr					
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<210> 44
 <211> 1925
 <212> DNA
 <213> Homo sapiens

<400> 44
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<210> 45

<211> 383

<212> PRT

<213> Homo sapiens

<400> 45

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His Ile Asp Thr Trp Glu Trp Asn Asp Val Thr Leu Tyr Gly Met Leu
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Asn Thr Leu Lys Asn Arg Asn Pro Asn Leu Lys Thr Leu Leu Ser Val
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100          105          110
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115          120          125
Thr His Gly Phe Asp Gly Leu Asp Leu Ala Trp Leu Tyr Pro Gly Arg
130          135          140
Arg Asp Lys Gln His Phe Thr Thr Leu Ile Lys Glu Met Lys Ala Glu
145          150          155          160
Phe Ile Lys Glu Ala Gln Pro Gly Lys Lys Gln Leu Leu Leu Ser Ala
165          170          175
Ala Leu Ser Ala Gly Lys Val Thr Ile Asp Ser Ser Tyr Asp Ile Ala
180          185          190
Lys Ile Ser Gln His Leu Asp Phe Ile Ser Ile Met Thr Tyr Asp Phe
195          200          205
His Gly Ala Trp Arg Gly Thr Thr Gly His His Ser Pro Leu Phe Arg
210          215          220
Gly Gln Glu Asp Ala Ser Pro Asp Arg Phe Ser Asn Thr Asp Tyr Ala
225          230          235          240
Val Gly Tyr Met Leu Arg Leu Gly Ala Pro Ala Ser Lys Leu Val Met
245          250          255
Gly Ile Pro Thr Phe Gly Arg Ser Phe Thr Leu Ala Ser Ser Glu Thr
260          265          270
Gly Val Gly Ala Pro Ile Ser Gly Pro Gly Ile Pro Gly Arg Phe Thr
275          280          285
Lys Glu Ala Gly Thr Leu Ala Tyr Tyr Glu Ile Cys Asp Phe Leu Arg

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Ala Leu Asp Leu Asp Asp Phe Gln Gly Ser Phe Cys Gly Gln Asp Leu				
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<210> 46
 <211> 1528
 <212> DNA
 <213> Homo sapiens

<400> 46

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<210> 47
 <211> 417
 <212> PRT
 <213> Homo sapiens

<400> 47

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	20	25	30
Arg Pro Glu Pro Val Arg Ala Ala Ser Glu Arg Arg Arg Leu Tyr Pro			
	35	40	45

Pro Ser Ala Glu Tyr Pro Asp Leu Arg Lys His Asn Asn Cys Met Ala
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 260 265 270
 Met Glu Lys Gly Gly Asn Met Lys Arg Val Phe Glu Arg Phe Cys Arg
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 Met Trp Asn Glu Arg Leu Gly Tyr Ile Leu Thr Cys Pro Ser Asn Leu
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 Gly Thr Gly Leu Arg Ala Gly Val His Ile Lys Leu Pro Leu Leu Ser
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 Ile Ser Asn Leu Asp Arg Leu Gly Lys Ser Glu Val Glu Leu Val Gln
 370 375 380
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<211> 2365

<212> DNA

<213> Homo sapiens

<400> 48

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 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Leu Trp Lys Ala Cys Val Thr Asp Ser Thr Gly Val Ser Asn Cys Lys
 50 55 60
 Asp Phe Pro Ser Met Leu Ala Leu Asp Gly Tyr Ile Gln Ala Cys Arg
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 Gly Leu Met Ile Ala Ala Val Ser Leu Gly Phe Phe Gly Ser Ile Phe
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 Ala Leu Phe Gly Met Lys Cys Thr Lys Val Gly Gly Ser Asp Lys Ala

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	130		135		140										
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Val	Ile	Phe	Cys	Phe	Ser	Ile	Ser	Asp	Asn	Asn	Lys	Thr	Pro	Arg	Tyr
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Thr	Tyr	Asn	Gly	Ala	Thr	Ser	Val	Met	Ser	Ser	Arg	Thr	Lys	Tyr	His
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Asn	Ala	Tyr	Val												
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 <213> Homo sapiens

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<210> 51
 <211> 305
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Arg His Leu Ser Gly Ala Arg Ala Gly Val Cys Pro Cys Cys His Pro
 50 55 60

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 <211> 1665
 <212> DNA
 <213> Homo sapiens

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 <211> 209
 <212> PRT
 <213> Homo sapiens

<400> 53

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Lys	Val	Tyr	Asp	Ser	Leu	Leu	Ala	Leu	Pro	Gln	Asp	Leu	Gln	Ala	Ala
65					70					75				80	
Arg	Ala	Leu	Val	Ile	Ile	Ser	Ile	Ile	Val	Ala	Ala	Leu	Gly	Val	Leu
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Leu	Ser	Val	Val	Gly	Gly	Lys	Cys	Thr	Asn	Cys	Leu	Glu	Asp	Glu	Ser
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<210> 54
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 <213> Homo sapiens

<400> 55

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Trp	Asp	Tyr	Ala	Ser	Asp	His	Gly	Glu	Lys	Lys	Leu	Ile	Ser	Val	Asp
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Thr	Glu	His	Ser	Asn	Ile	Tyr	Leu	Gln	Asn	Gly	Pro	Asp	Arg	Ile	Gly
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Arg	Leu	Tyr	Lys	Lys	Ala	Leu	Tyr	Leu	Gln	Tyr	Thr	Asp	Glu	Thr	Phe
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Arg	Thr	Thr	Ile	Glu	Lys	Pro	Val	Trp	Leu	Gly	Phe	Leu	Gly	Pro	Ile
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Ile	Lys	Ala	Glu	Thr	Gly	Asp	Lys	Val	Tyr	Val	His	Leu	Lys	Asn	Leu
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Ala	Ser	Arg	Pro	Tyr	Thr	Phe	His	Ser	His	Gly	Ile	Thr	Tyr	Tyr	Lys
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Glu	His	Glu	Gly	Ala	Ile	Tyr	Pro	Asp	Asn	Thr	Thr	Asp	Phe	Gln	Arg
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Ala	Thr	Glu	Glu	Gln	Ser	Pro	Gly	Glu	Gly	Asp	Gly	Asn	Cys	Val	Thr
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Arg	Ile	Tyr	His	Ser	His	Ile	Asp	Ala	Pro	Lys	Asp	Ile	Ala	Ser	Gly
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Leu	Ile	Gly	Pro	Leu	Ile	Ile	Cys	Lys	Lys	Asp	Ser	Leu	Asp	Lys	Glu
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Ser	Glu	Pro	Glu	Lys	Val	Asp	Lys	Asp	Asn	Glu	Asp	Phe	Gln	Glu	Ser
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Ser	Cys	Gln	Asn	Leu	Asn	His	Leu	Lys	Ala	Gly	Leu	Gln	Ala	Phe	Phe
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Gln	Val	Gln	Glu	Cys	Asn	Lys	Ser	Ser	Ser	Lys	Asp	Asn	Ile	Arg	Gly
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Lys	His	Val	Arg	His	Tyr	Tyr	Ile	Ala	Ala	Glu	Glu	Ile	Ile	Trp	Asn
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	450					455					460						
Phe	His	Asn	Lys	Gly	Ala	Tyr	Pro	Leu	Ser	Ile	Glu	Pro	Ile	Gly	Val		
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Arg	Phe	Asn	Lys	Asn	Asn	Glu	Gly	Thr	Tyr	Tyr	Ser	Pro	Asn	Tyr	Asn		
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Pro	Gln	Ser	Arg	Ser	Val	Pro	Pro	Ser	Ala	Ser	His	Val	Ala	Pro	Thr		
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Glu	Thr	Phe	Thr	Tyr	Glu	Trp	Thr	Val	Pro	Lys	Glu	Val	Gly	Pro	Thr		
	515						520					525					
Asn	Ala	Asp	Pro	Val	Cys	Leu	Ala	Lys	Met	Tyr	Tyr	Ser	Ala	Val	Asp		
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Glu	Phe	Tyr	Leu	Phe	Pro	Thr	Val	Phe	Asp	Glu	Asn	Glu	Ser	Leu	Leu		
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Leu	Glu	Asp	Asn	Ile	Arg	Met	Phe	Thr	Thr	Ala	Pro	Asp	Gln	Val	Asp		
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Lys	Glu	Asp	Glu	Asp	Phe	Gln	Glu	Ser	Asn	Lys	Met	His	Ser	Met	Asn		
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Tyr	Thr	Gly	Gly	Met	Lys	Gln	Lys	Tyr	Thr	Val	Asn	Gln	Cys	Arg	Arg		
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Gln	Ser	Glu	Asp	Ser	Thr	Phe	Tyr	Leu	Gly	Glu	Arg	Thr	Tyr	Tyr	Ile		
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Lys	Glu	Leu	His	His	Leu	Gln	Glu	Gln	Asn	Val	Ser	Asn	Ala	Phe	Leu		
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	770					775					780						
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Gly	Asp	Lys	Val	Lys	Ile	Ile	Phe	Lys	Asn	Met	Ala	Thr	Arg	Pro	Tyr		
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Ser	Ile	His	Ala	His	Gly	Val	Gln	Thr	Glu	Ser	Ser	Thr	Val	Thr	Pro		
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Thr	Leu	Pro	Gly	Glu	Thr	Leu	Thr	Tyr	Val	Trp	Lys	Ile	Pro	Glu	Arg		
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Lys Leu Glu Phe Ala Leu Leu Phe Leu Val Phe Asp Glu Asn Glu Ser						
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Trp Tyr Leu Asp Asp Asn Ile Lys Thr Tyr Ser Asp His Pro Glu Lys						
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Val Asn Lys Asp Asp Glu Glu Phe Ile Glu Ser Asn Lys Met His Ala						
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Ile Asn Gly Arg Met Phe Gly Asn Leu Gln Gly Leu Thr Met His Val						
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	980		985			990
Leu His Thr Val His Phe His Gly His Ser Phe Gln Tyr Lys His Arg						
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Thr Leu Glu Met Phe Pro Arg Thr Pro Gly Ile Trp Leu Leu His Cys						
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<211> 852

<212> PRT

<213> Homo sapiens

<400> 57

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Asn Glu Asp Phe Gln Glu Ser Asn Arg Met Tyr Ser Val Asn Gly Tyr
          35          40          45
Thr Phe Gly Ser Leu Pro Gly Leu Ser Met Cys Ala Glu Asp Arg Val
          50          55          60
Lys Trp Tyr Leu Phe Gly Met Gly Asn Glu Val Asp Val His Ala Ala
65          70          75          80
Phe Phe His Gly Gln Ala Leu Thr Asn Lys Asn Tyr Arg Ile Asp Thr
          85          90          95
Ile Asn Leu Phe Pro Ala Thr Leu Phe Asp Ala Tyr Met Val Ala Gln
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Asn Pro Gly Glu Trp Met Leu Ser Cys Gln Asn Leu Asn His Leu Lys
          115          120          125
Ala Gly Leu Gln Ala Phe Phe Gln Val Gln Glu Cys Asn Lys Ser Ser
          130          135          140
Ser Lys Asp Asn Ile Arg Gly Lys His Val Arg His Tyr Tyr Ile Ala
145          150          155          160
Ala Glu Glu Ile Ile Trp Asn Tyr Ala Pro Ser Gly Ile Asp Ile Phe
          165          170          175
Thr Lys Glu Asn Leu Thr Ala Pro Gly Ser Asp Ser Ala Val Phe Phe
          180          185          190
Glu Gln Gly Thr Thr Arg Ile Gly Gly Ser Tyr Lys Lys Leu Val Tyr
          195          200          205
Arg Glu Tyr Thr Asp Ala Ser Phe Thr Asn Arg Lys Glu Arg Gly Pro
210          215          220
Glu Glu Glu His Leu Gly Ile Leu Gly Pro Val Ile Trp Ala Glu Val

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Tyr	Tyr	Ser	Pro	Asn	Tyr	Asn	Pro	Gln	Ser	Arg	Ser	Val	Pro	Pro
		275					280					285		Ser
Ala	Ser	His	Val	Ala	Pro	Thr	Glu	Thr	Phe	Thr	Tyr	Glu	Trp	Thr
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Pro	Lys	Glu	Val	Gly	Pro	Thr	Asn	Ala	Asp	Pro	Val	Cys	Leu	Ala
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		340					345					350		Gly
Arg	Gln	Lys	Asp	Val	Asp	Lys	Glu	Phe	Tyr	Leu	Phe	Pro	Thr	Val
	355						360					365		Phe
Asp	Glu	Asn	Glu	Ser	Leu	Leu	Glu	Asp	Asn	Ile	Arg	Met	Phe	Thr
	370				375					380				
Thr	Ala	Pro	Asp	Gln	Val	Asp	Lys	Glu	Asp	Glu	Asp	Phe	Gln	Glu
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Asn	Lys	Met	His	Ser	Met	Asn	Gly	Phe	Met	Tyr	Gly	Asn	Gln	Pro
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Leu	Thr	Met	Cys	Lys	Gly	Asp	Ser	Val	Val	Trp	Tyr	Leu	Phe	Ser
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Gly	Asn	Glu	Ala	Asp	Val	His	Gly	Ile	Tyr	Phe	Ser	Gly	Asn	Thr
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Leu	Trp	Arg	Gly	Glu	Arg	Arg	Asp	Thr	Ala	Asn	Leu	Phe	Pro	Gln
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Ser	Leu	Thr	Leu	His	Met	Trp	Pro	Asp	Thr	Glu	Gly	Thr	Phe	Asn
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Glu	Cys	Leu	Thr	Thr	Asp	His	Tyr	Thr	Gly	Gly	Met	Lys	Gln	Lys
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Thr	Val	Asn	Gln	Cys	Arg	Arg	Gln	Ser	Glu	Asp	Ser	Thr	Phe	Tyr
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Pro	Gln	Leu	His	Ala	Asp	Val	Gly	Asp	Lys	Val	Lys	Ile	Ile	Phe
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Glu	Ser	Ser	Thr	Val	Thr	Pro	Thr	Leu	Pro	Gly	Glu	Thr	Leu	Thr
625					630					635				640
Val	Trp	Lys	Ile	Pro	Glu	Arg	Ser	Gly	Ala	Gly	Thr	Glu	Asp	Ser
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Cys	Ile	Pro	Trp	Ala	Tyr	Tyr	Ser	Thr	Val	Asp	Gln	Val	Lys	Asp
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Tyr	Ser	Gly	Leu	Ile	Gly	Pro	Leu	Ile	Val	Cys	Arg	Arg	Pro	Tyr
	675					680					685			Leu
Lys	Val	Phe	Asn	Pro	Arg	Arg	Lys	Leu	Glu	Phe	Ala	Leu	Leu	Phe

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Tyr Ser Asp His Pro Glu Lys Val Asn Lys Asp Asp Glu Glu Phe Ile		720
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Glu Ser Asn Lys Met His Ala Ile Asn Gly Arg Met Phe Gly Asn Leu		735
	740	745
Gln Gly Leu Thr Met His Val Gly Asp Glu Val Asn Trp Tyr Leu Met		750
	755	760
Gly Met Gly Asn Glu Ile Asp Leu His Thr Val His Phe His Gly His		765
	770	775
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Ile Phe Pro Gly Thr Tyr Gln Thr Leu Glu Met Phe Pro Arg Thr Pro		800
	805	810
Gly Ile Trp Leu Leu His Cys His Val Thr Asp His Ile His Ala Gly		815
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Thr Lys Ser Gly		845
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 actggagata aagtttatgt acacttaaaa aaccttgccct tagggcccta cacctttcat 360
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<210> 59

<211> 1065

<212> PRT

<213> Homo sapiens

<400> 59

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Trp Asp Tyr Ala Ser Asp His Gly Glu Lys Lys Leu Ile Ser Val Asp
      35           40           45
Thr Glu His Ser Asn Ile Tyr Leu Gln Asn Gly Pro Asp Arg Ile Gly
      50           55           60
Arg Leu Tyr Lys Lys Ala Leu Tyr Leu Gln Tyr Thr Asp Glu Thr Phe
      65           70           75           80
Arg Thr Thr Ile Glu Lys Pro Val Trp Leu Gly Phe Leu Gly Pro Ile
      85           90           95
Ile Lys Ala Glu Thr Gly Asp Lys Val Tyr Val His Leu Lys Asn Leu
      100          105          110
Ala Ser Arg Pro Tyr Thr Phe His Ser His Gly Ile Thr Tyr Tyr Lys
      115          120          125
Glu His Glu Gly Ala Ile Tyr Pro Asp Asn Thr Thr Asp Phe Gln Arg
      130          135          140
Ala Asp Asp Lys Val Tyr Pro Gly Glu Gln Tyr Thr Tyr Met Leu Leu
      145          150          155          160
Ala Thr Glu Glu Gln Ser Pro Gly Glu Gly Asp Gly Asn Cys Val Thr
      165          170          175
Arg Ile Tyr His Ser His Ile Asp Ala Pro Lys Asp Ile Ala Ser Gly
      180          185          190

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 210 215 220
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 225 230 235 240
 Ser Glu Pro Glu Lys Val Asp Lys Asp Asn Glu Asp Phe Gln Glu Ser
 245 250 255
 Asn Arg Met Tyr Ser Val Asn Gly Tyr Thr Phe Gly Ser Leu Pro Gly
 260 265 270
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 275 280 285
 Gly Asn Glu Val Asp Val His Ala Ala Phe Phe His Gly Gln Ala Leu
 290 295 300
 Thr Asn Lys Asn Tyr Arg Ile Asp Thr Ile Asn Leu Phe Pro Ala Thr
 305 310 315 320
 Leu Phe Asp Ala Tyr Met Val Ala Gln Asn Pro Gly Glu Trp Met Leu
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 Ser Cys Gln Asn Leu Asn His Leu Lys Ala Gly Leu Gln Ala Phe Phe
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 Gln Val Gln Glu Cys Asn Lys Ser Ser Ser Lys Asp Asn Ile Arg Gly
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 Pro Gly Ser Asp Ser Ala Val Phe Phe Glu Gln Gly Thr Thr Arg Ile
 405 410 415
 Gly Gly Ser Tyr Lys Lys Leu Val Tyr Arg Glu Tyr Thr Asp Ala Ser
 420 425 430
 Phe Thr Asn Arg Lys Glu Arg Gly Pro Glu Glu Glu His Leu Gly Ile
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 450 455 460
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 465 470 475 480
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 485 490 495
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 Lys Lys Gly Ser Leu His Ala Asn Gly Arg Gln Lys Asp Val Asp Lys
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<210> 60
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<212> DNA
<213> Homo sapiens
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<400> 60

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<210> 61

<211> 1090

<212> PRT

<213> Homo sapiens

<400> 61

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 20          25          30
Trp Asp Tyr Ala Ser Asp His Gly Glu Lys Lys Leu Ile Ser Val Asp
 35          40          45
Thr Glu His Ser Asn Ile Tyr Leu Gln Asn Gly Pro Asp Arg Ile Gly
 50          55          60
Arg Leu Tyr Lys Lys Ala Leu Tyr Leu Gln Tyr Thr Asp Glu Thr Phe
 65          70          75          80
Arg Thr Thr Ile Glu Lys Pro Val Trp Leu Gly Phe Leu Gly Pro Ile
 85          90          95
Ile Lys Ala Glu Thr Gly Asp Lys Val Tyr Val His Leu Lys Asn Leu
100          105          110
Ala Ser Arg Pro Tyr Thr Phe His Ser His Gly Ile Thr Tyr Tyr Lys
115          120          125
Glu His Glu Gly Ala Ile Tyr Pro Asp Asn Thr Thr Asp Phe Gln Arg
130          135          140
Ala Asp Asp Lys Val Tyr Pro Gly Glu Gln Tyr Thr Tyr Met Leu Leu
145          150          155          160
Ala Thr Glu Glu Gln Ser Pro Gly Glu Gly Asp Gly Asn Cys Val Thr
165          170          175
Arg Ile Tyr His Ser His Ile Asp Ala Pro Lys Asp Ile Ala Ser Gly
180          185          190
Leu Ile Gly Pro Leu Ile Ile Cys Lys Lys Asp Ser Leu Asp Lys Glu
195          200          205
Lys Glu Lys His Ile Asp Arg Glu Phe Val Val Met Phe Ser Val Val
210          215          220
Asp Glu Asn Phe Ser Trp Tyr Leu Glu Asp Asn Ile Lys Thr Tyr Cys
225          230          235          240
Ser Glu Pro Glu Lys Val Asp Lys Asp Asn Glu Asp Phe Gln Glu Ser
245          250          255
Asn Arg Met Tyr Ser Val Asn Gly Tyr Thr Phe Gly Ser Leu Pro Gly
260          265          270
Leu Ser Met Cys Ala Glu Asp Arg Val Lys Trp Tyr Leu Phe Gly Met
275          280          285
Gly Asn Glu Val Asp Val His Ala Ala Phe Phe His Gly Gln Ala Leu

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290	295	300
Thr Asn Lys Asn Tyr Arg Ile Asp Thr Ile Asn Leu Phe Pro Ala Thr		
305	310	315
Leu Phe Asp Ala Tyr Met Val Ala Gln Asn Pro Gly Glu Trp Met Leu		
	325	330
Ser Cys Gln Asn Leu Asn His Leu Lys Ala Gly Leu Gln Ala Phe Phe		
	340	345
Gln Val Gln Glu Cys Asn Lys Ser Ser Ser Lys Asp Asn Ile Arg Gly		
	355	360
Lys His Val Arg His Tyr Tyr Ile Ala Ala Glu Glu Ile Ile Trp Asn		
	370	375
Tyr Ala Pro Ser Gly Ile Asp Ile Phe Thr Lys Glu Asn Leu Thr Ala		
385	390	395
Pro Gly Ser Asp Ser Ala Val Phe Phe Glu Gln Gly Thr Thr Arg Ile		
	405	410
Gly Gly Ser Tyr Lys Lys Leu Val Tyr Arg Glu Tyr Thr Asp Ala Ser		
	420	425
Phe Thr Asn Arg Lys Glu Arg Gly Pro Glu Glu Glu His Leu Gly Ile		
	435	440
Leu Gly Pro Val Ile Trp Ala Glu Val Gly Asp Thr Ile Arg Val Thr		
	450	455
Phe His Asn Lys Gly Ala Tyr Pro Leu Ser Ile Glu Pro Ile Gly Val		
465	470	475
Arg Phe Asn Lys Asn Asn Glu Gly Thr Tyr Tyr Ser Pro Asn Tyr Asn		
	485	490
Pro Gln Ser Arg Ser Val Pro Pro Ser Ala Ser His Val Ala Pro Thr		
	500	505
Glu Thr Phe Thr Tyr Glu Trp Thr Val Pro Lys Glu Val Gly Pro Thr		
	515	520
Asn Ala Asp Pro Val Cys Leu Ala Lys Met Tyr Tyr Ser Ala Val Asp		
	530	535
Pro Thr Lys Asp Ile Phe Thr Gly Leu Ile Gly Pro Met Lys Ile Cys		
545	550	555
Lys Lys Gly Ser Leu His Ala Asn Gly Arg Gln Lys Asp Val Asp Lys		
	565	570
Glu Phe Tyr Leu Phe Pro Thr Val Phe Asp Glu Asn Glu Ser Leu Leu		
	580	585
Leu Glu Asp Asn Ile Arg Met Phe Thr Thr Ala Pro Asp Gln Val Asp		
	595	600
Lys Glu Asp Glu Asp Phe Gln Glu Ser Asn Lys Met His Ser Met Asn		
	610	615
Gly Phe Met Tyr Gly Asn Gln Pro Gly Leu Thr Met Cys Lys Gly Asp		
625	630	635
Ser Val Val Trp Tyr Leu Phe Ser Ala Gly Asn Glu Ala Asp Val His		
	645	650
Gly Ile Tyr Phe Ser Gly Asn Thr Tyr Leu Trp Arg Gly Glu Arg Arg		
	660	665
Asp Thr Ala Asn Leu Phe Pro Gln Thr Ser Leu Thr Leu His Met Trp		
	675	680
Pro Asp Thr Glu Gly Thr Phe Asn Val Glu Cys Leu Thr Thr Asp His		
	690	695
Tyr Thr Gly Gly Met Lys Gln Lys Tyr Thr Val Asn Gln Cys Arg Arg		
705	710	715
Gln Ser Glu Asp Ser Thr Phe Tyr Leu Gly Glu Arg Thr Tyr Tyr Ile		
	725	730
Ala Ala Val Glu Val Glu Trp Asp Tyr Ser Pro Gln Arg Glu Trp Glu		
	740	745
Lys Glu Leu His His Leu Gln Glu Gln Asn Val Ser Asn Ala Phe Leu		
	750	

755	760	765
Asp Lys Gly Glu Phe Tyr Ile Gly Ser Lys Tyr Lys Lys Val Val Tyr		
770	775	780
Arg Gln Tyr Thr Asp Ser Thr Phe Arg Val Pro Val Glu Arg Lys Ala		
785	790	795
Glu Glu Glu His Leu Gly Ile Leu Gly Pro Gln Leu His Ala Asp Val		
805	810	815
Gly Asp Lys Val Lys Ile Ile Phe Lys Asn Met Ala Thr Arg Pro Tyr		
820	825	830
Ser Ile His Ala His Gly Val Gln Thr Glu Ser Ser Thr Val Thr Pro		
835	840	845
Thr Leu Pro Gly Glu Thr Leu Thr Tyr Val Trp Lys Ile Pro Glu Arg		
850	855	860
Ser Gly Ala Gly Thr Glu Asp Ser Ala Cys Ile Pro Trp Ala Tyr Tyr		
865	870	875
Ser Thr Val Asp Gln Val Lys Asp Leu Tyr Ser Gly Leu Ile Gly Pro		
885	890	895
Leu Ile Val Cys Arg Arg Pro Tyr Leu Lys Val Phe Asn Pro Arg Arg		
900	905	910
Lys Leu Glu Phe Ala Leu Leu Phe Leu Val Phe Asp Glu Asn Glu Ser		
915	920	925
Trp Tyr Leu Asp Asp Asn Ile Lys Thr Tyr Ser Asp His Pro Glu Lys		
930	935	940
Val Asn Lys Asp Asp Glu Glu Phe Ile Glu Ser Asn Lys Met His Ala		
945	950	955
Ile Asn Gly Arg Met Phe Gly Asn Leu Gln Gly Leu Thr Met His Val		
965	970	975
Gly Asp Glu Val Asn Trp Tyr Leu Met Gly Met Gly Asn Glu Ile Asp		
980	985	990
Leu His Thr Val His Phe His Gly His Ser Phe Gln Tyr Lys His Arg		
995	1000	1005
Gly Val Tyr Ser Ser Asp Val Phe Asp Ile Phe Pro Gly Thr Tyr Gln		
1010	1015	1020
Thr Leu Glu Met Phe Pro Arg Thr Pro Gly Ile Trp Leu Leu His Cys		
1025	1030	1035
His Val Thr Asp His Ile His Ala Gly Met Glu Thr Thr Tyr Thr Val		
1045	1050	1055
Leu Gln Asn Glu Ala Ser Ser Glu Thr His Arg Arg Ile Trp Asn Val		
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Lys Glu		
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 <211> 969
 <212> DNA
 <213> Homo sapiens

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<210> 63

<211> 138

<212> PRT

<213> Homo sapiens

<400> 63

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 20          25          30
Ala Val Ala Ala Ser Lys Pro Ala Val Glu Ile Lys Gln Glu Gly
 35          40          45
Asp Thr Phe Tyr Ile Lys Thr Ser Thr Thr Val Arg Thr Thr Glu Ile
 50          55          60
Asn Phe Lys Val Gly Glu Glu Phe Glu Glu Gln Thr Val Asp Gly Arg
 65          70          75          80
Pro Cys Lys Ser Leu Val Lys Trp Glu Ser Glu Asn Lys Met Val Cys
 85          90          95
Glu Gln Lys Leu Leu Lys Gly Glu Gly Pro Lys Thr Ser Trp Thr Arg
100          105          110
Glu Leu Thr Asn Asp Gly Glu Leu Ile Leu Thr Met Thr Ala Asp Asp
115          120          125
Val Val Cys Thr Arg Val Tyr Val Arg Glu
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<210> 64

<211> 927

<212> DNA

<213> Homo sapiens

<400> 64

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<212> PRT

<213> Homo sapiens

<400> 65

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<212> DNA

<213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

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<400> 70

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 Ser Pro Thr Gly Gly Ala Pro His Gly Tyr Cys Ser Pro Thr Ser Ala
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 Ser Tyr Gly Lys Ala Leu Asn Pro Tyr Gln Tyr Gln Tyr His Gly Val
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 Tyr Ala Ser Ser Tyr His Gln Tyr Gly Gly Ala Tyr Asn Arg Val Pro
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 Ser Ala Thr Asn Gln Pro Glu Lys Glu Val Thr Glu Pro Glu Val Arg
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 Thr Gln Thr Gln Val Lys Ile Trp Phe Gln Asn Lys Arg Ser Lys Ile
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 Lys Lys Ile Met Lys Asn Gly Glu Met Pro Pro Glu His Ser Pro Ser
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 Ser Ser Asp Pro Met Ala Cys Asn Ser Pro Gln Ser Pro Ala Val Trp

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Ala Ser Trp Tyr Thr Ser Ala Ala Ser Ser Ile Asn Ser His Leu Pro				
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Tyr				

<210> 72
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 <212> DNA
 <213> Homo sapiens

<400> 72

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<210> 73
 <211> 434
 <212> PRT
 <213> Homo sapiens

<400> 73

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 Phe Pro Gln Ser Gln Tyr Pro Gln Tyr Tyr Gly Ser Ser Tyr Asn Pro
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 Pro Tyr Val Pro Ala Ser Ser Ile Cys Pro Ser Pro Leu Ser Thr Ser
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 Thr Tyr Val Leu Gln Glu Ala Ser His Asn Val Pro Asn Gln Ser Ser
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 Glu Ser Leu Ala Gly Glu Tyr Asn Thr His Asn Gly Pro Ser Thr Pro
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 Asn Glu Ile Glu Arg Val Phe Val Trp Asp Leu Asp Glu Thr Ile Ile
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 Ile Phe His Ser Leu Leu Thr Gly Thr Phe Ala Ser Arg Tyr Gly Lys
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 Asp Thr Thr Thr Ser Val Arg Ile Gly Leu Met Met Glu Glu Met Ile
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 Phe Asn Leu Ala Asp Thr His Leu Phe Phe Asn Asp Leu Glu Asp Cys
 210 215 220
 Asp Gln Ile His Val Asp Asp Val Ser Ser Asp Asp Asn Gly Gln Asp
 225 230 235 240
 Leu Ser Thr Tyr Asn Phe Ser Ala Asp Gly Phe His Ser Ser Ala Pro
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 Gly Ala Asn Leu Cys Leu Gly Ser Gly Val His Gly Gly Val Asp Trp
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 Cys Val Asn Val Leu Val Thr Thr Thr Gln Leu Ile Pro Ala Leu Ala
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<210> 74
 <211> 1907
 <212> DNA
 <213> Homo sapiens

<400> 74
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 <212> PRT
 <213> Homo sapiens

<400> 75
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 Met Ser Leu Glu Gly Thr Glu Lys Ala Ser Trp Leu Gly Glu Gln Pro
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 Gln Phe Trp Ser Lys Thr Gln Val Leu Asp Trp Ile Ser Tyr Gln Val
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 Glu Lys Asn Lys Tyr Asp Ala Ser Ala Ile Asp Phe Ser Arg Cys Asp

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<400> 77

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Lys	Ala	Glu	Leu	Ala	Asp	His	Gln	Lys	Phe	Pro	Cys	Ser	Thr	Pro	His
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Gln	His	Lys	His	Ile	His	Ser	Ser	Val	Lys	Pro	Phe	Ile	Cys	Glu	Val
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<211> 3978

<212> DNA

<213> Homo sapiens

<220>

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Lys Arg Lys Leu Thr Asp Pro Leu Glu Ala Leu Lys Glu Lys Tyr Leu
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<211> 4923

<212> DNA

<213> Homo sapiens

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<211> 1042

<212> PRT

<213> Homo sapiens

<400> 83

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Glu Asn Asp Leu Gln Glu Ile His Thr Ile Gln Glu Cys Lys Glu Cys
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Gln His Lys His Ile His Ser Ser Val Lys Pro Phe Ile Cys Glu Val
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 Phe Arg Ala Pro Pro Asn Ala Leu Pro Glu Asn Leu Leu Arg Lys Gly
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 Lys Glu Arg Tyr Thr Cys Arg Tyr Cys Gly Lys Ile Phe Pro Arg Ser
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 Arg His Val Arg Asn Ile His Asn Lys Glu Lys Pro Phe Lys Cys His
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<211> 4039

<212> DNA

<213> Homo sapiens

<400> 84

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 <213> Homo sapiens

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<211> 1385

<212> DNA

<213> Homo sapiens

<400> 86

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 <212> PRT
 <213> Homo sapiens

<400> 87

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<400> 88

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 <212> PRT
 <213> Homo sapiens

<400> 89

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<210> 91

<211> 625

<212> PRT

<213> Homo sapiens

<400> 91

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Asp Glu Ala Trp Lys Ser Tyr Leu Glu Asn Pro Leu Thr Ala Ala Thr
35          40          45
Lys Ala Met Met Ile Ile Asn Gly Asp Glu Asp Ser Ala Ala Ala Leu
50          55          60
Gly Leu Leu Tyr Asp Tyr Tyr Lys Val Pro Arg Asp Lys Arg Leu Leu
65          70          75          80
Ser Val Ser Lys Ala Ser Asp Ser Gln Glu Asp Gln Glu Lys Arg Asn
85          90          95
Cys Leu Gly Thr Ser Glu Ala Gln Ser Asn Leu Ser Gly Gly Glu Asn
100         105         110
Arg Val Gln Val Leu Lys Thr Val Pro Val Asn Leu Ser Leu Asn Gln
115         120         125
Asp His Leu Glu Asn Ser Lys Arg Glu Gln Tyr Ser Ile Ser Phe Pro
130         135         140
Glu Ser Ser Ala Ile Ile Pro Val Ser Gly Ile Thr Val Val Lys Ala
145         150         155         160
Glu Asp Phe Thr Pro Val Phe Met Ala Pro Pro Val His Tyr Pro Arg
165         170         175
Gly Asp Gly Glu Glu Gln Arg Val Val Ile Phe Glu Gln Thr Gln Tyr
180         185         190
Asp Val Pro Ser Leu Ala Thr His Ser Ala Tyr Leu Lys Asp Asp Gln
195         200         205
Arg Ser Thr Pro Asp Ser Thr Tyr Ser Glu Ser Phe Lys Asp Ala Ala
210         215         220
Thr Glu Lys Phe Arg Ser Ala Ser Val Gly Ala Glu Glu Tyr Met Tyr
225         230         235         240
Asp Gln Thr Ser Ser Gly Thr Phe Gln Tyr Thr Leu Glu Ala Thr Lys
245         250         255
Ser Leu Arg Gln Lys Gln Gly Glu Gly Pro Met Thr Tyr Leu Asn Lys
260         265         270
Gly Gln Phe Tyr Ala Ile Thr Leu Ser Glu Thr Gly Asp Asn Lys Cys
275         280         285
Phe Arg His Pro Ile Ser Lys Val Arg Ser Val Val Met Val Val Phe
290         295         300
Ser Glu Asp Lys Asn Arg Asp Glu Gln Leu Lys Tyr Trp Lys Tyr Trp
305         310         315         320
His Ser Arg Gln His Thr Ala Lys Gln Arg Val Leu Asp Ile Ala Asp
325         330         335
Tyr Lys Glu Ser Phe Asn Thr Ile Gly Asn Ile Glu Glu Ile Ala Tyr
340         345         350

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Asn Ala Val Ser Phe Thr Trp Asp Val Asn Glu Glu Ala Lys Ile Phe
 355 360 365
 Ile Thr Val Asn Cys Leu Ser Thr Asp Phe Ser Ser Gln Lys Gly Val
 370 375 380
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 385 390 395 400
 Arg Ser Asn Lys Pro Ile His Arg Ala Tyr Cys Gln Ile Lys Val Phe
 405 410 415
 Cys Asp Lys Gly Ala Glu Arg Lys Ile Arg Asp Glu Glu Gln Lys Gln
 420 425 430
 Asn Arg Lys Asn Gly Lys Gly Gln Ala Ser Gln Thr Gln Cys Asn Ser
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 Ser Ser Asp Gly Lys Leu Ala Ala Ile Pro Leu Gln Lys Lys Ser Asp
 450 455 460
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 Arg Met Phe Arg Pro Met Glu Glu Phe Gly Pro Val Pro Ser Lys
 515 520 525
 Gln Met Lys Glu Glu Gly Thr Lys Arg Val Leu Leu Tyr Val Arg Lys
 530 535 540
 Glu Thr Asp Asp Val Phe Asp Ala Leu Met Leu Lys Ser Pro Thr Val
 545 550 555 560
 Met Gly Leu Met Glu Ala Ile Ser Glu Lys Tyr Gly Leu Pro Val Glu
 565 570 575
 Lys Ile Ala Lys Leu Tyr Lys Lys Ser Lys Lys Gly Ile Leu Val Asn
 580 585 590
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 Leu Asn Met Glu Ser Met Val Glu Gly Phe Lys Val Thr Leu Met Glu
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 Ile
 625

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 <211> 2085
 <212> DNA
 <213> Homo sapiens

<400> 92
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<210> 93

<211> 301

<212> PRT

<213> Homo sapiens

<400> 93

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          20          25          30
Gly Glu Glu Glu Arg Ala His Gln Ser Ile Leu Thr Gln Arg Val His
          35          40          45
Trp Ala Glu Ala Leu Gln Lys Leu Asp Thr Ile Arg Thr Gly Leu Val
          50          55          60
Gly Met Leu Thr His Leu Asp Asp Leu Gln Leu Ile Gln Lys Glu Gln
          65          70          75          80
Glu Ile Phe Glu Arg Thr Glu Glu Ala Glu Gly Ile Leu Asp Pro Gln
          85          90          95
Glu Ser Glu Met Leu Asn Phe Asn Glu Lys Cys Thr Arg Ser Pro Leu
          100         105         110
Leu Thr Gln Leu Trp Ala Thr Ala Val Leu Gly Ser Leu Ser Gly Thr
          115         120         125
Glu Asp Ile Arg Ile Asp Glu Arg Thr Val Ser Pro Phe Leu Gln Leu
          130         135         140
Ser Asp Asp Arg Lys Thr Leu Thr Phe Ser Thr Lys Lys Ser Lys Ala
          145         150         155         160
Cys Ala Asp Gly Pro Glu Arg Phe Asp His Trp Pro Asn Ala Leu Ala
          165         170         175
Ala Thr Ser Phe Gln Asn Gly Leu His Ala Trp Met Val Asn Val Gln
          180         185         190
Asn Ser Cys Ala Tyr Lys Val Gly Val Ala Ser Gly His Leu Pro Arg
          195         200         205
Lys Gly Ser Gly Ser Asp Cys Arg Leu Gly His Asn Ala Phe Ser Trp
          210         215         220
Val Phe Ser Arg Tyr Asp Gln Glu Phe Arg Phe Ser His Asn Gly Gln
          225         230         235         240

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111

His Glu Pro Leu Gly Leu Leu Arg Gly Pro Ala Gln Leu Gly Val Val
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 Leu Asp Leu Gln Val Gln Glu Leu Leu Phe Tyr Glu Pro Ala Ser Gly
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 275 280 285
 Val Phe Ala Val Ala Asp Gln Thr Ile Ser Ile Val Arg
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<210> 94
 <211> 2317
 <212> DNA
 <213> Homo sapiens

<400> 94
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<210> 95
 <211> 626

<212> PRT

<213> Homo sapiens

<400> 95

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Leu	Thr	Cys	Leu	Cys	Pro	Gln	Cys	Leu	Ser	Val	Glu	Asp	Ala	Leu	Gly	35	40	45	
Leu	Gly	Glu	Pro	Glu	Gly	Ser	Gly	Leu	Pro	Pro	Gly	Pro	Val	Leu	Glu	50	55	60	
Ala	Arg	Tyr	Val	Ala	Arg	Leu	Ser	Ala	Ala	Ala	Val	Leu	Tyr	Leu	Ser	65	70	75	80
Asn	Pro	Glu	Gly	Thr	Cys	Glu	Asp	Ala	Arg	Ala	Gly	Leu	Trp	Ala	Ser	85	90	95	
His	Ala	Asp	His	Leu	Leu	Ala	Leu	Leu	Glu	Ser	Pro	Lys	Ala	Leu	Thr	100	105	110	
Pro	Gly	Leu	Ser	Trp	Leu	Leu	Gln	Arg	Met	Gln	Ala	Arg	Ala	Ala	Gly	115	120	125	
Gln	Thr	Pro	Lys	Thr	Ala	Cys	Val	Asp	Ile	Pro	Gln	Leu	Leu	Glu	Glu	130	135	140	
Ala	Val	Gly	Ala	Gly	Ala	Pro	Gly	Ser	Ala	Gly	Gly	Val	Leu	Ala	Ala	145	150	155	160
Leu	Leu	Asp	His	Val	Arg	Ser	Gly	Ser	Cys	Phe	His	Ala	Leu	Pro	Ser	165	170	175	
Pro	Gln	Tyr	Phe	Val	Asp	Phe	Val	Phe	Gln	Gln	His	Ser	Ser	Glu	Val	180	185	190	
Pro	Met	Thr	Leu	Ala	Glu	Leu	Ser	Ala	Leu	Met	Gln	Arg	Leu	Gly	Val	195	200	205	
Gly	Arg	Glu	Ala	His	Ser	Asp	His	Ser	His	Arg	His	Arg	Gly	Ala	Ser	210	215	220	
Ser	Arg	Asp	Pro	Val	Pro	Leu	Ile	Ser	Ser	Ser	Asn	Ser	Ser	Ser	Val	225	230	235	240
Trp	Asp	Thr	Val	Cys	Leu	Ser	Ala	Arg	Asp	Val	Met	Ala	Ala	Tyr	Gly	245	250	255	
Leu	Ser	Glu	Gln	Ala	Gly	Val	Thr	Pro	Glu	Ala	Trp	Ala	Gln	Leu	Ser	260	265	270	
Pro	Ala	Leu	Gln	Gln	Gln	Leu	Ser	Gly	Ala	Tyr	Thr	Ser	Gln	Ser		275	280	285	
Arg	Pro	Pro	Val	Gln	Asp	Gln	Leu	Ser	Gln	Ser	Glu	Arg	Tyr	Leu	Tyr	290	295	300	
Gly	Ser	Leu	Ala	Thr	Leu	Leu	Ile	Cys	Leu	Cys	Ala	Val	Phe	Gly	Leu	305	310	315	320
Leu	Leu	Leu	Thr	Cys	Thr	Gly	Cys	Arg	Gly	Val	Ala	His	Tyr	Ile	Leu	325	330	335	
Gln	Thr	Phe	Leu	Ser	Leu	Ala	Val	Gly	Ala	Leu	Thr	Gly	Asp	Ala	Val	340	345	350	
Leu	His	Leu	Thr	Pro	Lys	Val	Leu	Gly	Leu	His	Thr	His	Ser	Glu	Glu	355	360	365	
Gly	Leu	Ser	Pro	Gln	Pro	Thr	Trp	Arg	Leu	Leu	Ala	Met	Leu	Ala	Gly	370	375	380	
Leu	Tyr	Ala	Phe	Phe	Leu	Phe	Glu	Asn	Leu	Phe	Asn	Leu	Leu	Leu	Pro	385	390	395	400
Arg	Asp	Pro	Glu	Asp	Leu	Glu	Asp	Gly	Pro	Cys	Gly	His	Ser	Ser	His	405	410	415	
Ser	His	Gly	Gly	His	Ser	His	Gly	Val	Ser	Leu	Gln	Leu	Ala	Pro	Ser	420	425	430	

Glu Leu Arg Gln Pro Lys Pro Pro His Glu Gly Ser Arg Ala Asp Leu
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 Val Ala Glu Glu Ser Pro Glu Leu Leu Asn Pro Glu Pro Arg Arg Leu
 450 455 460
 Ser Pro Glu Leu Arg Leu Leu Pro Tyr Met Ile Thr Leu Gly Asp Ala
 465 470 475 480
 Val His Asn Phe Ala Asp Gly Leu Ala Val Gly Ala Ala Phe Ala Ser
 485 490 495
 Ser Trp Lys Thr Gly Leu Ala Thr Ser Leu Ala Val Phe Cys His Glu
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 Leu Pro His Glu Leu Gly Asp Phe Ala Ala Leu Leu His Ala Gly Leu
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 Phe Ala Gly Leu Thr Trp His Ser Arg Leu Glu Ser Ala Arg Arg Ala
 545 550 555 560
 Arg Pro Gly Ser Trp Gln Trp Pro Pro Ala Cys Ser Leu Arg Ser Thr
 565 570 575
 Leu Arg His Ala Pro Gly Asp Val Glu Ser Thr Gly Pro Ala Ala Pro
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 Ser Cys Cys Cys Pro Cys Thr Arg Met Thr Ser Pro Ser Asp Thr
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 Leu Pro
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<210> 96
 <211> 2761
 <212> DNA
 <213> Homo sapiens

<400> 96
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<210> 97

<211> 422

<212> PRT

<213> Homo sapiens

<400> 97

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Ala Thr Leu Ser Lys Val Glu Gly Thr Asp Val Thr Gly Ile Glu Glu
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Val Val Ile Pro Lys Lys Lys Thr Trp Asp Lys Val Ala Val Leu Gln
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Ala Leu Ala Ser Thr Val Asn Arg Asp Thr Thr Ala Val Pro Tyr Val
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Phe Gln Asp Asp Pro Tyr Leu Met Pro Ala Ser Ser Leu Glu Ser Arg
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Ser Phe Leu Leu Ala Lys Lys Ser Gly Glu Asn Val Ala Lys Phe Ile
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Ile Asn Ser Tyr Pro Lys Tyr Phe Gln Lys Asp Ile Ala Glu Pro His
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Ser Glu Ala Ala Leu Lys Glu Arg Ile Glu Leu Arg Lys Val Lys Ala
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Leu Glu Thr Thr Asn Ser Leu Leu Asp Leu Leu Cys Tyr Tyr Gly Asp
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Gln Glu Pro Ser Thr Asp Tyr His Phe Gln Gln Thr Gly Gln Ser Glu
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 Gly Met Val Lys His Arg Ala Tyr Glu Gln Ala Leu Asn Leu Tyr Thr
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<211> 697

<212> PRT

<213> Homo sapiens

<400> 99

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Ala Gly Leu Cys Glu Gln Ala Arg Ser Cys Arg Phe Tyr Ser Gly Ser
 35          40          45
Ala Thr Leu Ser Lys Val Glu Gly Thr Asp Val Thr Gly Ile Glu Glu
 50          55          60
Val Val Ile Pro Lys Lys Lys Thr Trp Asp Lys Val Ala Val Leu Gln
 65          70          75          80
Ala Leu Ala Ser Thr Val Asn Arg Asp Thr Thr Ala Val Pro Tyr Val
 85          90          95
Phe Gln Asp Asp Pro Tyr Leu Met Pro Ala Ser Ser Leu Glu Ser Arg
100          105          110
Ser Phe Leu Leu Ala Lys Lys Ser Gly Glu Asn Val Ala Lys Phe Ile
115          120          125
Ile Asn Ser Tyr Pro Lys Tyr Phe Gln Lys Asp Ile Ala Glu Pro His
130          135          140
Ile Pro Cys Leu Met Pro Glu Tyr Phe Glu Pro Gln Ile Lys Asp Ile
145          150          155          160
Ser Glu Ala Ala Leu Lys Glu Arg Ile Glu Leu Arg Lys Val Lys Ala
165          170          175
Ser Val Asp Met Phe Asp Gln Leu Leu Gln Ala Gly Thr Thr Val Ser
180          185          190
Leu Glu Thr Thr Asn Ser Leu Leu Asp Leu Leu Cys Tyr Tyr Gly Asp
195          200          205
Gln Glu Pro Ser Thr Asp Tyr His Phe Gln Gln Thr Gly Gln Ser Glu
210          215          220
Ala Leu Glu Glu Glu Asn Asp Glu Thr Ser Arg Arg Lys Ala Gly His

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 <212> DNA
 <213> Homo sapiens

<400> 100

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 <213> Homo sapiens

<400> 101

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  35          40          45
Tyr Ser Lys Phe Phe Asp Leu Ile Cys Leu Met Glu Gln Ile Asp Val
  50          55          60
Thr Leu Lys Trp Tyr Glu Asp Leu Ile Pro Ser Ala Tyr Phe Pro His
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 <212> DNA
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<210> 103

<211> 414

<212> PRT

<213> Homo sapiens

<400> 103

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Met Ser Ser Pro Asp Ala Gly Tyr Ala Ser Asp Asp Gln Ser Gln Thr
 1          5          10          15
Gln Ser Ala Leu Pro Ala Val Met Ala Gly Leu Gly Pro Cys Pro Trp
          20          25          30
Ala Glu Ser Leu Ser Pro Ile Gly Asp Met Lys Val Lys Gly Glu Ala
          35          40          45
Pro Ala Asn Ser Gly Ala Pro Ala Gly Ala Ala Gly Arg Ala Lys Gly
          50          55          60
Glu Ser Arg Ile Arg Arg Pro Met Asn Ala Phe Met Val Trp Ala Lys
65          70          75          80
Asp Glu Arg Lys Arg Leu Ala Gln Gln Asn Pro Asp Leu His Asn Ala
          85          90          95
Glu Leu Ser Lys Met Leu Gly Lys Ser Trp Lys Ala Leu Thr Leu Ala
          100          105          110
Glu Lys Arg Pro Phe Val Glu Glu Ala Glu Arg Leu Arg Val Gln His
          115          120          125
Met Gln Asp His Pro Asn Tyr Lys Tyr Arg Pro Arg Arg Arg Lys Gln
          130          135          140
Val Lys Arg Leu Lys Arg Val Glu Gly Gly Phe Leu His Gly Leu Ala
145          150          155          160
Glu Pro Gln Ala Ala Ala Leu Gly Pro Glu Gly Gly Arg Val Ala Met
          165          170          175
Asp Gly Leu Gly Leu Gln Phe Pro Glu Gln Gly Phe Pro Ala Gly Pro
          180          185          190
Pro Leu Leu Pro Pro His Met Gly Gly His Tyr Arg Asp Cys Gln Ser
          195          200          205
Leu Gly Ala Pro Pro Leu Asp Gly Tyr Pro Leu Pro Thr Pro Asp Thr
          210          215          220
Ser Pro Leu Asp Gly Val Asp Pro Asp Pro Ala Phe Phe Ala Ala Pro
225          230          235          240
Met Pro Gly Asp Cys Pro Ala Ala Gly Thr Tyr Ser Tyr Ala Gln Val
          245          250          255
Ser Asp Tyr Ala Gly Pro Pro Glu Pro Pro Ala Gly Pro Met His Pro
          260          265          270
Arg Leu Gly Pro Glu Pro Ala Gly Pro Ser Ile Pro Gly Leu Leu Ala
          275          280          285
Pro Pro Ser Ala Leu His Val Tyr Tyr Gly Ala Met Gly Ser Pro Gly
          290          295          300
Ala Gly Gly Gly Arg Gly Phe Gln Met Gln Pro Gln His Gln His Gln
305          310          315          320
His Gln His Gln His His Pro Pro Gly Pro Gly Gln Pro Ser Pro Pro
          325          330          335
Pro Glu Ala Leu Pro Cys Arg Asp Gly Thr Asp Pro Ser Gln Pro Ala

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	340		345		350
Glu Leu Leu Gly Glu Val Asp Arg Thr Glu Phe Glu Gln Tyr Leu His					
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Phe Val Cys Lys Pro Glu Met Gly Leu Pro Tyr Gln Gly His Asp Ser					
	370		375		380
Gly Val Asn Leu Pro Asp Ser His Gly Ala Ile Ser Ser Val Val Ser					
385		390		395	400
Asp Ala Ser Ser Ala Val Tyr Tyr Cys Asn Tyr Pro Asp Val					
	405		410		

<210> 104
 <211> 2398
 <212> DNA
 <213> Homo sapiens

<400> 104

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cgctcagcc tcatgagtag ctgggactac aggtgtgggt gtccacgccc agctaatttt 180
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122

<210> 105
 <211> 232
 <212> PRT
 <213> Homo sapiens

<400> 105

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Met Asp Ala Ser Ile Met Asp Gly Lys Asp Leu Ser Ala Gly Ala Val
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Ser Ala Val Gln Cys Ile Ala Asn Pro Ile Lys Leu Ala Arg Leu Val
          20          25          30
Met Glu Lys Thr Pro His Cys Phe Leu Thr Asp Gln Gly Ala Ala Gln
          35          40          45
Phe Ala Ala Ala Met Gly Val Pro Glu Ile Pro Gly Glu Lys Leu Val
          50          55          60
Thr Glu Arg Asn Lys Lys Arg Leu Glu Lys Glu Lys His Glu Lys Gly
65          70          75          80
Ala Gln Lys Thr Asp Cys Gln Lys Asn Leu Gly Thr Val Gly Ala Val
          85          90          95
Ala Leu Asp Cys Lys Gly Asn Val Ala Tyr Ala Thr Ser Thr Gly Gly
          100         105         110
Ile Val Asn Lys Met Val Gly Arg Val Gly Asp Ser Pro Cys Leu Gly
          115         120         125
Ala Gly Gly Tyr Ala Asp Asn Asp Ile Gly Ala Val Ser Thr Thr Gly
          130         135         140
His Gly Glu Ser Ile Leu Lys Val Asn Leu Ala Arg Leu Thr Leu Phe
145         150         155         160
His Ile Glu Gln Gly Lys Thr Val Glu Glu Ala Ala Asp Leu Ser Leu
          165         170         175
Gly Tyr Met Lys Ser Arg Val Lys Gly Leu Gly Gly Leu Ile Val Val
          180         185         190
Ser Lys Thr Gly Asp Trp Val Ala Lys Trp Thr Ser Thr Ser Met Pro
          195         200         205
Trp Ala Ala Ala Lys Asp Gly Lys Leu His Phe Gly Ile Asp Pro Asp
          210         215         220
Asp Thr Thr Ile Thr Asp Leu Pro
225         230

```

<210> 106
 <211> 1811
 <212> DNA
 <213> Homo sapiens

<400> 106

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cacagtcact actgtcgctt cagctgggaa cattggggag gatggaatcc agagctgcac 240
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aggcttggtc catgagttca aagaaggcaa agatgagctg tcggagcagg atgaaatgtt 360
cagaggcccg acagcagtgt ttgctgatca agtgatagtt ggcaatgcct ctttgccgct 420
gaaaaacgtg caactcacag atgctggcac ctacaaatgt tatatcatca cttctaaagg 480
caaggggaat gctaaccttg agtataaaac tggagccttc agcatgccgg aagtgaatgt 540
ggactataat gccagctcag agaccttgcg gtgtgaggct ccccgatggt tccccagcc 600
cacagtggtc tgggcatccc aagttgacca gggagccaac ttctcggaag tctccaatac 660
cagctttgag ctgaactctg agaatgtgac catgaagggt gtgtctgtgc tctacaatgt 720
tacgatcaac aacacatact cctgtatgat tgaaaatgac attgccaaag caacagggga 780
tatcaaagtg acagaatcgg agatcaaaag gcggagtcac ctacagctgc taaactcaaa 840

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gttaaccact gccttcctgg accttggagc cacggtgact gtattacatg ttgttataga 1740
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<210> 107

<211> 282

<212> PRT

<213> Homo sapiens

<400> 107

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Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile
1           5           10          15
Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser
20          25          30
Gly Arg His Ser Ile Thr Val Thr Thr Val Ala Ser Ala Gly Asn Ile
35          40          45
Gly Glu Asp Gly Ile Gln Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu
50          55          60
Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val
65          70          75          80
His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met
85          90          95
Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn
100         105         110
Ala Ser Leu Arg Leu Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr
115         120         125
Lys Cys Tyr Ile Ile Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu
130         135         140
Tyr Lys Thr Gly Ala Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn
145         150         155         160
Ala Ser Ser Glu Thr Leu Arg Cys Glu Ala Pro Arg Trp Phe Pro Gln
165         170         175
Pro Thr Val Val Trp Ala Ser Gln Val Asp Gln Gly Ala Asn Phe Ser
180         185         190
Glu Val Ser Asn Thr Ser Phe Glu Leu Asn Ser Glu Asn Val Thr Met
195         200         205
Lys Val Val Ser Val Leu Tyr Asn Val Thr Ile Asn Asn Thr Tyr Ser
210         215         220
Cys Met Ile Glu Asn Asp Ile Ala Lys Ala Thr Gly Asp Ile Lys Val
225         230         235         240
Thr Glu Ser Glu Ile Lys Arg Arg Ser His Leu Gln Leu Leu Asn Ser
245         250         255
Lys Ala Ser Leu Cys Val Ser Ser Phe Phe Ala Ile Ser Trp Ala Leu
260         265         270

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Leu Pro Leu Ser Pro Tyr Leu Met Leu Lys
275 280

<210> 108
<211> 2611
<212> DNA
<213> Homo sapiens

<400> 108
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cagatggcca tggatgaagt tggacagact ggaataatat gtccaagttt ttccagtatg 180
gatggcgatg caccactaat gagaatacct attcaaaccg taccctgatg ggcaactgga 240
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gatacaaatg cacagaaaag tcaacttaca tgaatagcta ttcaaagcct taaattgggc 480
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a 2611

<210> 109
<211> 150
<212> PRT

<213> Homo sapiens

<400> 109

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Met Ala Ala Ser Gln Cys Leu Cys Cys Ser Lys Phe Leu Phe Gln Arg
 1           5           10           15
Gln Asn Leu Ala Cys Phe Leu Thr Asn Pro His Cys Gly Ser Leu Val
      20           25           30
Asn Ala Asp Gly His Gly Glu Val Trp Thr Asp Trp Asn Asn Met Ser
      35           40           45
Lys Phe Phe Gln Tyr Gly Trp Arg Cys Thr Thr Asn Glu Asn Thr Tyr
      50           55           60
Ser Asn Arg Thr Leu Met Gly Asn Trp Asn Gln Glu Arg Tyr Asp Leu
      65           70           75           80
Arg Asn Ile Val Gln Pro Lys Pro Leu Pro Ser Gln Phe Gly His Tyr
      85           90           95
Phe Glu Thr Thr Tyr Asp Thr Ser Tyr Asn Asn Lys Met Pro Leu Ser
      100          105          110
Thr His Arg Phe Lys Arg Glu Pro His Trp Phe Pro Gly His Gln Pro
      115          120          125
Glu Leu Asp Pro Pro Arg Tyr Lys Cys Thr Glu Lys Ser Thr Tyr Met
      130          135          140
Asn Ser Tyr Ser Lys Pro
      145          150

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<210> 110

<211> 1032

<212> DNA

<213> Homo sapiens

<400> 110

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<210> 111

<211> 257

<212> PRT

<213> Homo sapiens

<400> 111

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Met Ala Gln Arg Met Thr Thr Gln Leu Leu Leu Leu Val Trp Val
 1           5           10           15

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Ala Val Val Gly Glu Ala Gln Thr Arg Ile Ala Trp Ala Arg Thr Glu
 20 25 30
 Leu Leu Asn Val Cys Met Asn Ala Lys His His Lys Glu Lys Pro Gly
 35 40 45
 Pro Glu Asp Lys Leu His Glu Gln Cys Arg Pro Trp Arg Lys Asn Ala
 50 55 60
 Cys Cys Ser Thr Asn Thr Ser Gln Glu Ala His Lys Asp Val Ser Tyr
 65 70 75 80
 Leu Tyr Arg Phe Asn Trp Asn His Cys Gly Glu Met Ala Pro Ala Cys
 85 90 95
 Lys Arg His Phe Ile Gln Asp Thr Cys Leu Tyr Glu Cys Ser Pro Asn
 100 105 110
 Leu Gly Pro Trp Ile Gln Gln Val Asp Gln Ser Trp Arg Lys Glu Arg
 115 120 125
 Val Leu Asn Val Pro Leu Cys Lys Glu Asp Cys Glu Gln Trp Trp Glu
 130 135 140
 Asp Cys Arg Thr Ser Tyr Thr Cys Lys Ser Asn Trp His Lys Gly Trp
 145 150 155 160
 Asn Trp Thr Ser Gly Phe Asn Lys Cys Ala Val Gly Ala Ala Cys Gln
 165 170 175
 Pro Phe His Phe Tyr Phe Pro Thr Pro Thr Val Leu Cys Asn Glu Ile
 180 185 190
 Trp Thr His Ser Tyr Lys Val Ser Asn Tyr Ser Arg Gly Ser Gly Arg
 195 200 205
 Cys Ile Gln Met Trp Phe Asp Pro Ala Gln Gly Asn Pro Asn Glu Glu
 210 215 220
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 225 230 235 240
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<210> 112
 <211> 1104
 <212> DNA
 <213> Homo sapiens

<400> 112
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1104

<210> 113

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<213> Homo sapiens

<400> 113

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<211> 1331

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 115

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<211> 858

<212> DNA

<213> Homo sapiens

<400> 116

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<211> 243

<212> PRT

<213> Homo sapiens

<400> 117

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35           40           45
Asp Glu Leu Tyr Gly Gln Cys Ser Pro Trp Lys Lys Asn Ala Cys Cys
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Thr Ala Ser Thr Ser Gln Glu Leu His Lys Asp Thr Ser Arg Leu Tyr
65           70           75           80

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129

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 His Phe Ile Gln Asp Ser Cys Leu Tyr Glu Cys Ser Pro Asn Leu Gly
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 Asn Val Pro Leu Cys Lys Glu Asp Cys Glu Arg Trp Trp Glu Asp Cys
 130 135 140
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 Glu Ser Tyr Phe Pro Thr Pro Ala Ala Leu Cys Glu Gly Leu Trp Ser
 180 185 190
 His Ser Phe Lys Val Ser Asn Tyr Ser Arg Gly Ser Gly Arg Cys Ile
 195 200 205
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 <211> 1362
 <212> DNA
 <213> Homo sapiens

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 <212> PRT
 <213> Homo sapiens

<400> 119

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<212> DNA

<213> Homo sapiens

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[illegible]

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 <211> 1474
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 <213> Homo sapiens

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<210> 123
 <211> 320
 <212> PRT
 <213> Homo sapiens

<400> 123
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 Pro Gly Leu Glu Lys Ala His Phe Trp Val Gly Phe Pro Leu Leu Ser
 20 25 30
 Met Tyr Val Val Ala Met Cys Gly Asn Cys Ile Val Val Phe Ile Val
 35 40 45
 Arg Thr Glu Arg Ser Leu His Ala Pro Met Tyr Leu Phe Leu Cys Met
 50 55 60
 Leu Ala Ala Ile Asp Leu Ala Leu Ser Thr Ser Thr Met Pro Lys Ile
 65 70 75 80
 Leu Ala Leu Phe Trp Phe Asp Ser Arg Glu Ile Ser Ile Glu Ala Cys
 85 90 95
 Leu Thr Gln Met Phe Phe Ile His Ala Leu Ser Ala Ile Glu Ser Thr
 100 105 110
 Ile Leu Leu Ala Met Ala Phe Asp Arg Tyr Val Ala Ile Cys His Pro
 115 120 125
 Leu Arg His Ala Ala Val Leu Asn Asn Thr Val Thr Ala Gln Ile Gly

134

130	135	140
Ile Val Ala Val Val Arg Gly Ser Leu Phe Phe Pro Leu Pro Leu		
145	150	155
Leu Ile Lys Arg Leu Ala Phe Cys His Ser Asn Val Leu Ser His Ser		160
	165	170
Tyr Cys Val His Gln Asp Val Met Lys Leu Ala Tyr Ala Asp Thr Leu		175
	180	185
Pro Asn Val Val Tyr Gly Leu Thr Ala Ile Leu Leu Val Met Gly Val		190
	195	200
Asp Val Met Phe Ile Ser Leu Ser Tyr Phe Leu Ile Ile Arg Thr Val		205
	210	215
Leu Gln Leu Pro Ser Lys Ser Glu Arg Ala Lys Ala Phe Gly Thr Cys		220
225	230	235
Val Ser His Ile Gly Val Val Leu Ala Phe Tyr Val Pro Leu Ile Gly		240
	245	250
Leu Ser Val Val His Arg Phe Gly Asn Ser Leu His Pro Ile Val Arg		255
	260	265
Val Val Met Gly Asp Ile Tyr Leu Leu Leu Pro Pro Val Ile Asn Pro		270
	275	280
Ile Ile Tyr Gly Ala Lys Thr Lys Gln Ile Arg Thr Arg Val Leu Ala		285
	290	295
Met Phe Lys Ile Ser Cys Asp Lys Asp Leu Gln Ala Val Gly Gly Lys		300
305	310	315
		320

<210> 124

<211> 2205

<212> DNA

<213> Homo sapiens

<400> 124

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acaactggtt ccgttaagcc cctctctcgc tcagacgcc a tgagctgga tctgtctcca 240
cctcatctta gcagctctcc ggaagacctt tggccagccc ctgggacccc tcttgggact 300
ccccggcccc ctgatacccc tctgcctgag gaggtaaaga ggtcccagcc tctcctcatc 360
ccaaccaccg gcaggaaact tcgagaggag gagaggcgtg ccacctccct cccctctatc 420
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acccaactct ggttccacgg gcgcatttcc cgtgaggaga gccagcggct tattggacag 1560
cagggtctgg tagacggcct gttcctggtc cgggagagtc agcgggaacc ccagggtctt 1620

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ctcgtggagt tccaccagct gaaccgcggc atcctgccgt gcttgctgcg ccattgctgc 1800
acgcgggtgg ccctctgacc aggccgtgga ctggctcatg cctcagcccg ccttcaggct 1860
gcccgcgcgc cctccaccca tccagtggac tctggggcgc ggccacaggg gacgggatga 1920
ggagcgggag gggtccgcca ctccagtttt ctcctctgct tctttgcctc cctcagatag 1980
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ccccctctcc ttctcctagc tctggaggtg ctgctctagg gcaggggaatt atgggagaag 2100
tgggggcagc ccaggcggtt tcacgcccc cactttgtac agaccgagag gccagttgat 2160
ctgctctgtt ttatactagt gacaataaag attatttttt gatac 2205

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<210> 125

<211> 532

<212> PRT

<213> Homo sapiens

<400> 125

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Met Glu Leu Asp Leu Ser Pro Pro His Leu Ser Ser Ser Pro Glu Asp
 1          5          10          15
Leu Trp Pro Ala Pro Gly Thr Pro Pro Gly Thr Pro Arg Pro Pro Asp
          20          25          30
Thr Pro Leu Pro Glu Glu Val Lys Arg Ser Gln Pro Leu Leu Ile Pro
          35          40          45
Thr Thr Gly Arg Lys Leu Arg Glu Glu Arg Arg Ala Thr Ser Leu
          50          55          60
Pro Ser Ile Pro Asn Pro Phe Pro Glu Leu Cys Ser Pro Pro Ser Gln
          65          70          75          80
Ser Pro Ile Leu Gly Gly Pro Ser Ser Ala Arg Gly Leu Leu Pro Arg
          85          90          95
Asp Ala Ser Arg Pro His Val Val Lys Val Tyr Ser Glu Asp Gly Ala
          100          105          110
Cys Arg Ser Val Glu Val Ala Ala Gly Ala Thr Ala Arg His Val Cys
          115          120          125
Glu Met Leu Val Gln Arg Ala His Ala Leu Ser Asp Glu Thr Trp Gly
          130          135          140
Leu Val Glu Cys His Pro His Leu Ala Leu Glu Arg Gly Leu Glu Asp
          145          150          155          160
His Glu Ser Val Val Glu Val Gln Ala Ala Trp Pro Val Gly Gly Asp
          165          170          175
Ser Arg Phe Val Phe Arg Lys Asn Phe Ala Lys Tyr Glu Leu Phe Lys
          180          185          190
Ser Ser Pro His Ser Leu Phe Pro Glu Lys Met Val Ser Ser Cys Leu
          195          200          205
Asp Ala His Thr Gly Ile Ser His Glu Asp Leu Ile Gln Asn Phe Leu
          210          215          220
Asn Ala Gly Ser Phe Pro Glu Ile Gln Gly Phe Leu Gln Leu Arg Gly
          225          230          235          240
Ser Gly Arg Lys Leu Trp Lys Arg Phe Phe Cys Phe Leu Arg Arg Ser
          245          250          255
Gly Leu Tyr Tyr Ser Thr Lys Gly Thr Ser Lys Asp Pro Arg His Leu
          260          265          270
Gln Tyr Val Ala Asp Val Asn Glu Ser Asn Val Tyr Val Val Thr Gln
          275          280          285
Gly Arg Lys Leu Tyr Gly Met Pro Thr Asp Phe Gly Phe Cys Val Lys
          290          295          300
Pro Asn Lys Leu Arg Asn Gly His Lys Gly Leu Arg Ile Phe Cys Ser
          305          310          315          320
Glu Asp Glu Gln Ser Arg Thr Cys Trp Leu Ala Ala Phe Arg Leu Phe

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<210> 126
<211> 1619
<212> DNA
<213> Homo sapiens
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<400>	126					
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ggctggggcc	ggcccaggag	cttccccagg	gctcccaccg	tccatggcgg	tgcgggggga	180
gcccgcacat	ccctgtcctt	caccacgcgg	agctgcccac	cccctggagg	gtcttgggggt	240
tctggaagaa	gcagccccct	actaggcgga	aatgggaagg	ccaccatgca	gaatctcaac	300
gaccgccttg	cctcctacct	ggagaagggt	cgcgcccttg	aggaggccaa	catgaagctg	360
gaaagccgca	tcctgaaatg	gcaccagcag	agagatcctg	gcagtaagaa	agattattcc	420
cagtatgagg	aaaacatcac	acacctgcag	gagcagatag	tggatggtaa	gatgaccaat	480
gtcagatta	ttctttctcat	tgacaatgcc	aggatggcag	tggatgactt	caacctcaag	540
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accttagaca	acctgaccat	tgtcacaaca	gacctagaac	aggaggtgga	aggaatgagg	660
aaagagctca	ttctcatgaa	ggagcaccat	gagcaggaaa	tggaggagca	tcattgtgcc	720
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ctggaggata	tgagacaaga	atatgagctt	ataataaaga	agaagcatcg	agacttggac	840
acttggtata	aagaacagtc	tgcagccatg	tcccaggagg	cagccagtcc	agccactgtg	900
cagagcagac	aaggtgacat	ccacgaactg	aagcgcacat	tccaggccct	ggagattgac	960
ctgcaggcac	agtacagcac	gaaatctgct	ttggaaaaca	tggtattccga	gacctagctt	1020
cggtactctc	gcaagctcca	ggacatgcaa	gagatcatct	cccactatga	ggaggaactg	1080
acgcagctac	gccacgaact	ggagcggcag	aacaatgaat	accaagtgtc	gctgggcac	1140
aaaaccacc	tggagaagga	aatcaccacg	taccgacggc	tcctggaggg	agagagtga	1200
gggacacggg	aagaatcaaa	gtcagagcatg	aaagtgtctg	caactccaaa	gatcaaggcc	1260
ataaccagg	agaccatcaa	cggaagatta	gttctttgtc	aagtgaatga	aatccaaaag	1320
cacgcacatg	accaatgaaa	gtttccgcct	gttgtaaagt	ctattttccc	ccaaggaaa	1380

tccttgacaca gacaccagtg agtgagttct aaaagataacc cttggaatta tcagactcag 1440
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 tattgcactt ttctaataca agtgcgagtt tatgagggta aagctctact ttcctactgc 1560
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<210> 127

<211> 422

<212> PRT

<213> Homo sapiens

<400> 127

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Gly	Ala	Gly	Gly	Gly	Trp	Gly	Arg	Pro	Arg	Ser	Phe	Pro	Arg	Ala	Pro
			20					25					30		
Thr	Val	His	Gly	Gly	Ala	Gly	Gly	Ala	Arg	Ile	Ser	Leu	Ser	Phe	Thr
		35					40					45			
Thr	Arg	Ser	Cys	Pro	Pro	Pro	Gly	Gly	Ser	Trp	Gly	Ser	Gly	Arg	Ser
	50					55					60				
Ser	Pro	Leu	Leu	Gly	Gly	Asn	Gly	Lys	Ala	Thr	Met	Gln	Asn	Leu	Asn
65				70					75					80	
Asp	Arg	Leu	Ala	Ser	Tyr	Leu	Glu	Lys	Val	Arg	Ala	Leu	Glu	Glu	Ala
			85						90					95	
Asn	Met	Lys	Leu	Glu	Ser	Arg	Ile	Leu	Lys	Trp	His	Gln	Gln	Arg	Asp
			100					105					110		
Pro	Gly	Ser	Lys	Lys	Asp	Tyr	Ser	Gln	Tyr	Glu	Glu	Asn	Ile	Thr	His
		115					120					125			
Leu	Gln	Glu	Gln	Ile	Val	Asp	Gly	Lys	Met	Thr	Asn	Ala	Gln	Ile	Ile
	130					135					140				
Leu	Leu	Ile	Asp	Asn	Ala	Arg	Met	Ala	Val	Asp	Asp	Phe	Asn	Leu	Lys
145				150					155					160	
Tyr	Glu	Asn	Glu	His	Ser	Phe	Lys	Lys	Asp	Leu	Glu	Ile	Glu	Val	Glu
			165						170					175	
Gly	Leu	Arg	Arg	Thr	Leu	Asp	Asn	Leu	Thr	Ile	Val	Thr	Thr	Asp	Leu
		180					185						190		
Glu	Gln	Glu	Val	Glu	Gly	Met	Arg	Lys	Glu	Leu	Ile	Leu	Met	Lys	Glu
	195					200						205			
His	His	Glu	Gln	Glu	Met	Glu	Glu	His	His	Val	Pro	Ser	Asp	Phe	Asn
	210				215						220				
Val	Asn	Val	Lys	Val	Asp	Thr	Gly	Pro	Arg	Glu	Asp	Leu	Ile	Lys	Val
225				230					235					240	
Leu	Glu	Asp	Met	Arg	Gln	Glu	Tyr	Glu	Leu	Ile	Ile	Lys	Lys	Lys	His
			245					250						255	
Arg	Asp	Leu	Asp	Thr	Trp	Tyr	Lys	Glu	Gln	Ser	Ala	Ala	Met	Ser	Gln
		260					265						270		
Glu	Ala	Ala	Ser	Pro	Ala	Thr	Val	Gln	Ser	Arg	Gln	Gly	Asp	Ile	His
	275					280						285			
Glu	Leu	Lys	Arg	Thr	Phe	Gln	Ala	Leu	Glu	Ile	Asp	Leu	Gln	Ala	Gln
	290					295					300				
Tyr	Ser	Thr	Lys	Ser	Ala	Leu	Glu	Asn	Met	Leu	Ser	Glu	Thr	Gln	Ser
305				310					315					320	
Arg	Tyr	Ser	Cys	Lys	Leu	Gln	Asp	Met	Gln	Glu	Ile	Ile	Ser	His	Tyr
			325					330						335	
Glu	Glu	Glu	Leu	Thr	Gln	Leu	Arg	His	Glu	Leu	Glu	Arg	Gln	Asn	Asn
		340				345						350			
Glu	Tyr	Gln	Val	Leu	Leu	Gly	Ile	Lys	Thr	His	Leu	Glu	Lys	Glu	Ile
	355					360						365			
Thr	Thr	Tyr	Arg	Arg	Leu	Leu	Glu	Gly	Glu	Ser	Glu	Gly	Thr	Arg	Glu

138

370 375 380
 Glu Ser Lys Ser Ser Met Lys Val Ser Ala Thr Pro Lys Ile Lys Ala
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 Ile Thr Gln Glu Thr Ile Asn Gly Arg Leu Val Leu Cys Gln Val Asn
 405 410 415
 Glu Ile Gln Lys His Ala
 420

<210> 128
 <211> 1359
 <212> DNA
 <213> Homo sapiens

<400> 128
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 aatgctttat tttctaaata tccagcctca agttcgggtt tcgctaccgg agccttccca 180
 gaacaaactt cttgtgcgtt tgcttccaac cccagcgcc cggttatgg agcgggttcg 240
 ggcgcttcct tcgcgggctc gatgcagggc ttgtaccccg gcgggggggg catggcgggc 300
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 gcgggcgcca aggagcagag ggactcggac ttggcgggcc agagtaactt ccgatctac 480
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<210> 129
 <211> 217
 <212> PRT
 <213> Homo sapiens

<400> 129
 Met Ser Ser Leu Tyr Tyr Ala Asn Ala Leu Phe Ser Lys Tyr Pro Ala
 1 5 10 15
 Ser Ser Ser Val Phe Ala Thr Gly Ala Phe Pro Glu Gln Thr Ser Cys
 20 25 30
 Ala Phe Ala Ser Asn Pro Gln Arg Pro Gly Tyr Gly Ala Gly Ser Gly
 35 40 45
 Ala Ser Phe Ala Gly Ser Met Gln Gly Leu Tyr Pro Gly Gly Gly Gly
 50 55 60
 Met Ala Gly Gln Ser Ala Ala Gly Val Tyr Ala Gly Tyr Gly Leu
 65 70 75 80
 Glu Pro Ser Ser Phe Asn Met His Cys Ala Pro Phe Glu Gln Asn Leu
 85 90 95
 Ser Gly Val Cys Pro Gly Asp Ser Ala Lys Ala Ala Gly Ala Lys Glu

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<210> 130
<211> 1257
<212> DNA
<213> Homo sapiens
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<400> 130						
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agcaaaaggc	gcagctccgg	cagagggagg	tggtagacct	gtataatgga	atgtgcttac	300
aagggccagc	aggagtgcct	ggtcgagacg	ggagccctgg	ggccaatggc	attccgggta	360
cacctgggat	cccaggtcgg	gatggattca	aaggagaaaa	gggggaatgt	ctgaggggaa	420
gctttgagga	gtcctggaca	cccaactaca	agcagtgttc	atggagttca	ttgaattatg	480
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tgctttgga	tggttcactt	aaatgacatt	ttaaataagt	ttatgtatac	atctgaatga	960
aaagcaaaag	taaatatggt	tcacagccaa	agtgtagatt	cacactgttt	ttaaatctag	1020
cattattcat	tttgcttcaa	tcaaagatgg	tttcaatatt	tttttagt	ggttagaata	1080
ctttcttcat	agtcacattc	tctcaacctc	taatttggaa	tattgtttgt	gtctttttgt	1140
ttttctctta	gtatagcatt	tttaaaaaaa	tataaaagct	accaatcttt	gtacaatttg	1200
taaatgttaa	qaattttttt	tatatctgtt	aaataaaaaa	tatttccaac	aacctta	1257

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<210> 131
<211> 278
<212> PRT
<213> Homo sapiens
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<400> 131
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 1          5          10          15
Val Pro Leu Leu Gly Leu Leu Arg Leu Gln Leu Arg Ala Ala Arg Gln
          20          25          30
Pro Gly Ala Met Arg Pro Gln Gly Pro Ala Ala Ser Pro Gln Arg Leu
          35          40          45
Arg Gly Leu Leu Leu Leu Leu Leu Leu Gln Leu Pro Ala Pro Ser Ser

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140

50	55	60
Ala Ser Glu Ile Pro Lys Gly Lys Gln Lys Ala Gln Leu Arg Gln Arg		
65	70	75
Glu Val Val Asp Leu Tyr Asn Gly Met Cys Leu Gln Gly Pro Ala Gly		80
	85	90
Val Pro Gly Arg Asp Gly Ser Pro Gly Ala Asn Gly Ile Pro Gly Thr		95
	100	105
Pro Gly Ile Pro Gly Arg Asp Gly Phe Lys Gly Glu Lys Gly Glu Cys		110
	115	120
Leu Arg Glu Ser Phe Glu Glu Ser Trp Thr Pro Asn Tyr Lys Gln Cys		125
	130	135
Ser Trp Ser Ser Leu Asn Tyr Gly Ile Asp Leu Gly Lys Ile Ala Glu		140
145	150	155
Cys Thr Phe Thr Lys Met Arg Ser Asn Ser Ala Leu Arg Val Leu Phe		160
	165	170
Ser Gly Ser Leu Arg Leu Lys Cys Arg Asn Ala Cys Cys Gln Arg Trp		175
	180	185
Tyr Phe Thr Phe Asn Gly Ala Glu Cys Ser Gly Pro Leu Pro Ile Glu		190
	195	200
Ala Ile Ile Tyr Leu Asp Gln Gly Ser Pro Glu Met Asn Ser Thr Ile		205
	210	215
Asn Ile His Arg Thr Ser Ser Val Glu Gly Leu Cys Glu Gly Ile Gly		220
225	230	235
Ala Gly Leu Val Asp Val Ala Ile Trp Val Gly Thr Cys Ser Asp Tyr		240
	245	250
Pro Lys Gly Asp Ala Ser Thr Gly Trp Asn Ser Val Ser Arg Ile Ile		255
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Ile Glu Glu Leu Pro Lys		270
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<210> 132

<211> 1177

<212> DNA

<213> Homo sapiens

<400> 132

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141

<210> 133
 <211> 210
 <212> PRT
 <213> Homo sapiens

<400> 133

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          20           25           30
Asp Gly Ser Pro Gly Ala Asn Gly Ile Pro Gly Thr Pro Gly Ile Pro
          35           40           45
Gly Arg Asp Gly Phe Lys Gly Glu Lys Gly Glu Cys Leu Arg Glu Ser
          50           55           60
Phe Glu Glu Ser Trp Thr Pro Asn Tyr Lys Gln Cys Ser Trp Ser Ser
65           70           75           80
Leu Asn Tyr Gly Ile Asp Leu Gly Lys Ile Ala Glu Cys Thr Phe Thr
          85           90           95
Lys Met Arg Ser Asn Ser Ala Leu Arg Val Leu Phe Ser Gly Ser Leu
          100          105          110
Arg Leu Lys Cys Arg Asn Ala Cys Cys Gln Arg Trp Tyr Phe Thr Phe
          115          120          125
Asn Gly Ala Glu Cys Ser Gly Pro Leu Pro Ile Glu Ala Ile Ile Tyr
          130          135          140
Leu Asp Gln Gly Ser Pro Glu Met Asn Ser Thr Ile Asn Ile His Arg
145          150          155          160
Thr Ser Ser Val Glu Gly Leu Cys Glu Gly Ile Gly Ala Gly Leu Val
          165          170          175
Asp Val Ala Ile Trp Val Gly Thr Cys Ser Asp Tyr Pro Lys Gly Asp
          180          185          190
Ala Ser Thr Gly Trp Asn Ser Val Ser Arg Ile Ile Ile Glu Glu Leu
          195          200          205
Pro Lys
          210

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<210> 134
 <211> 1340
 <212> DNA
 <213> Homo sapiens

<400> 134

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142

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cttttgtttt ttctcttagt atagcatttt taaaaaata taaaagctac caatctttgt 1260
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<210> 135

<211> 243

<212> PRT

<213> Homo sapiens

<400> 135

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20      25      30
Ile Pro Lys Gly Lys Gln Lys Ala Gln Leu Arg Gln Arg Glu Val Val
35      40      45
Asp Leu Tyr Asn Gly Met Cys Leu Gln Gly Pro Ala Gly Val Pro Gly
50      55      60
Arg Asp Gly Ser Pro Gly Ala Asn Gly Ile Pro Gly Thr Pro Gly Ile
65      70      75      80
Pro Gly Arg Asp Gly Phe Lys Gly Glu Lys Gly Glu Cys Leu Arg Glu
85      90      95
Ser Phe Glu Glu Ser Trp Thr Pro Asn Tyr Lys Gln Cys Ser Trp Ser
100     105     110
Ser Leu Asn Tyr Gly Ile Asp Leu Gly Lys Ile Ala Glu Cys Thr Phe
115     120     125
Thr Lys Met Arg Ser Asn Ser Ala Leu Arg Val Leu Phe Ser Gly Ser
130     135     140
Leu Arg Leu Lys Cys Arg Asn Ala Cys Cys Gln Arg Trp Tyr Phe Thr
145     150     155     160
Phe Asn Gly Ala Glu Cys Ser Gly Pro Leu Pro Ile Glu Ala Ile Ile
165     170     175
Tyr Leu Asp Gln Gly Ser Pro Glu Met Asn Ser Thr Ile Asn Ile His
180     185     190
Arg Thr Ser Ser Val Glu Gly Leu Cys Glu Gly Ile Gly Ala Gly Leu
195     200     205
Val Asp Val Ala Ile Trp Val Gly Thr Cys Ser Asp Tyr Pro Lys Gly
210     215     220
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225     230     235     240
Leu Pro Lys

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<210> 136

<211> 5519

<212> DNA

<213> Homo sapiens

<400> 136

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tggcgggctg gccctgcga gaggcggact cagggctgct ggatgctccg tccttggccg 180
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tggcaggccc	gggcgcggcc	tcgtgccgaa	ttcggcacga	gggggtttcg	gcggccggga	420
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aagcaactaa	caaaacactg	tgataataag	gattattcag	tatgcagttt	gcaggatata	540
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<210> 137

<211> 765

<212> PRT

<213> Homo sapiens

<400> 137

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 20          25          30
Ala Arg His Val Phe Thr Gly Glu Lys Val Ala Val Lys Val Ile Asp
 35          40          45
Lys Thr Lys Leu Asp Thr Leu Ala Thr Gly His Leu Phe Gln Glu Val
 50          55          60
Arg Cys Met Lys Leu Val Gln His Pro Asn Ile Val Arg Leu Tyr Glu
 65          70          75          80
Val Ile Asp Thr Gln Thr Lys Leu Tyr Leu Ile Leu Glu Leu Gly Asp
 85          90          95
Glu Gly Asp Met Phe Asp Tyr Ile Met Lys His Glu Glu Gly Leu Asn
100          105          110
Glu Asp Leu Pro Lys Lys Tyr Phe Ala Gln Ile Val His Ala Ile Ser
115          120          125
Tyr Cys His Lys Leu His Val Val His Arg Asp Leu Lys Pro Glu Asn
130          135          140
Val Val Phe Phe Glu Lys Gln Gly Leu Val Lys Leu Thr Asp Phe Gly
145          150          155          160
Phe Ser Asn Lys Phe Gln Pro Gly Lys Lys Leu Thr Thr Ser Cys Gly

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145

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Ala	Pro	Ala	Val	Asp	Ile	Trp	Ser	Leu	Gly	Val	Ile	Leu	Phe	Met	Leu
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Val	Cys	Gly	Gln	Pro	Pro	Phe	Gln	Glu	Ala	Asn	Asp	Ser	Glu	Thr	Leu
	210					215					220				
Thr	Met	Ile	Met	Asp	Cys	Lys	Tyr	Thr	Val	Pro	Ser	His	Val	Ser	Lys
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Glu	Cys	Lys	Asp	Leu	Ile	Thr	Arg	Met	Leu	Gln	Arg	Asp	Pro	Lys	Arg
				245					250					255	
Arg	Ala	Ser	Leu	Glu	Glu	Ile	Glu	Asn	His	Pro	Trp	Leu	Gln	Gly	Val
			260					265					270		
Asp	Pro	Ser	Pro	Ala	Thr	Lys	Tyr	Asn	Ile	Pro	Leu	Val	Ser	Tyr	Lys
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Asn	Leu	Ser	Glu	Glu	Glu	His	Asn	Ser	Ile	Ile	Gln	Arg	Met	Val	Leu
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Gly	Asp	Ile	Ala	Asp	Arg	Asp	Ala	Ile	Val	Glu	Ala	Leu	Glu	Thr	Asn
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Arg	Tyr	Asn	His	Ile	Thr	Ala	Thr	Tyr	Phe	Leu	Leu	Ala	Glu	Arg	Ile
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Pro	Glu	Leu	Ala	Gly	Pro	Ala	Leu	Ser	Thr	Val	Pro	Pro	Ala	Ser	Leu
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Lys	Ser	Ala	Pro	Val	Leu	Asn	Gln	Ile	Phe	Glu	Glu	Gly	Glu	Ser	Asp
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Thr	Tyr	Ser	Trp	His	Arg	Arg	Asp	Ser	Ser	Glu	Gly	Pro	Pro	Gly	Ser
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Glu	Gly	Asp	Gly	Gly	Gly	Gln	Ser	Lys	Pro	Ser	Asn	Ala	Ser	Gly	Gly
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Val	Asp	Lys	Ala	Ser	Pro	Ser	Glu	Asn	Asn	Ala	Gly	Gly	Gly	Ser	Pro
	595						600					605			
Ser	Ser	Gly	Ser	Gly	Gly	Asn	Pro	Thr	Asn	Thr	Ser	Gly	Thr	Thr	Arg
	610					615					620				
Arg	Cys	Ala	Gly	Pro	Ser	Asn	Ser	Met	Gln	Leu	Ala	Ser	Arg	Ser	Ala

146

625		630		635		640									
Gly	Glu	Leu	Val	Glu	Ser	Leu	Lys	Leu	Met	Ser	Leu	Cys	Leu	Gly	Ser
				645					650					655	
Gln	Leu	His	Gly	Ser	Thr	Lys	Tyr	Ile	Ile	Asp	Pro	Gln	Asn	Gly	Leu
			660					665					670		
Ser	Phe	Ser	Ser	Val	Lys	Val	Gln	Glu	Lys	Ser	Thr	Trp	Lys	Met	Cys
			675				680					685			
Ile	Ser	Ser	Thr	Gly	Asn	Ala	Gly	Gln	Val	Pro	Ala	Val	Gly	Gly	Ile
			690			695				700					
Lys	Phe	Phe	Ser	Asp	His	Met	Ala	Asp	Thr	Thr	Thr	Glu	Leu	Glu	Arg
705					710				715					720	
Ile	Lys	Ser	Lys	Asn	Leu	Lys	Asn	Asn	Val	Leu	Gln	Leu	Pro	Leu	Cys
			725				730						735		
Glu	Lys	Thr	Ile	Ser	Val	Asn	Ile	Gln	Arg	Asn	Pro	Lys	Glu	Gly	Leu
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<210> 138

<211> 2029

<212> DNA

<213> Homo sapiens

<400> 138

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<400> 139															
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Ala	Pro	Ser 35	Gln	Asn	Ile	Phe	Phe 40	Ser	Pro	Val	Ser	Ile	Ser	Met	Ser
Leu	Ala	Met	Leu	Ser	Leu	Gly 55	Ala	Gly	Ser	Ser	Thr 60	Lys	Met	Gln	Ile
Leu 65	Glu	Gly	Leu	Gly 70	Asn	Leu	Gln	Lys	Ser 75	Ser	Glu	Lys	Glu	Leu 80	
His	Arg	Gly	Phe	Gln 85	Gln	Leu	Leu	Gln	Glu 90	Leu	Asn	Gln	Pro	Arg 95	Asp
Gly	Phe	Gln	Leu	Ser	Leu	Gly	Asn	Ala 105	Leu	Phe	Thr	Asp	Leu	Val	Val
Asp	Leu	Gln 115	Asp	Thr	Phe	Val	Ser	Ala 120	Met	Lys	Thr	Leu	Tyr	Leu	Ala
Asp	Thr 130	Phe	Pro	Thr	Asn	Phe 135	Arg	Asp	Ser	Ala	Gly 140	Ala	Met	Lys	Gln
Ile 145	Asn	Asp	Tyr	Val	Ala	Lys 150	Gln	Thr	Lys	Gly 155	Lys	Ile	Val	Asp	Leu 160
Leu	Lys	Asn	Leu	Asp 165	Ser	Asn	Ala	Val	Val 170	Ile	Met	Val	Asn	Tyr 175	Ile
Phe	Phe	Lys	Ala	Lys 180	Trp	Glu	Thr	Ser 185	Phe	Asn	His	Lys	Gly	Thr	Gln
Glu	Gln	Asp 195	Phe	Tyr	Val	Thr	Ser	Glu 200	Thr	Val	Val	Arg	Val	Pro	Met
Met	Ser 210	Arg	Glu	Asp	Gln	Tyr 215	His	Tyr	Leu	Leu	Asp 220	Arg	Asn	Leu	Ser
Cys 225	Arg	Val	Val	Gly	Val	Pro 230	Tyr	Gln	Gly	Asn	Ala	Thr	Ala	Leu	Phe 240
Ile	Leu	Pro	Ser	Glu 245	Gly	Lys	Met	Gln	Gln	Val	Glu	Asn	Gly	Leu	Ser
Glu	Lys	Thr	Leu	Arg 260	Lys	Trp	Leu	Lys 265	Met	Phe	Lys	Lys	Arg	Gln	Leu
Glu	Leu	Tyr 275	Leu	Pro	Lys	Phe	Ser	Ile 280	Glu	Gly	Ser	Tyr	Gln	Leu	Glu
Lys	Val 290	Leu	Pro	Ser	Leu	Gly 295	Ile	Ser	Asn	Val	Phe	Thr	Ser	His	Ala
Asp 305	Leu	Ser	Gly	Ile	Ser	Asn 310	His	Ser	Asn	Ile	Gln	Val	Ser	Glu	Met
Val	His	Lys	Ala	Val	Val	Glu	Val	Asp 330	Glu	Ser	Gly	Thr	Arg	Ala	Ala
Ala	Ala	Thr	Gly 340	Thr	Ile	Phe	Thr	Phe 345	Arg	Ser	Ala	Arg	Leu	Asn	Ser
Gln	Arg	Leu 355	Val	Phe	Asn	Arg	Pro	Phe 360	Leu	Met	Phe	Ile	Val	Asp	Asn
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<210> 140
 <211> 2058
 <212> DNA
 <213> Homo sapiens

<400> 140
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 gaacaatgga agtgacaaca agattgacat ggaatgatga aaatcatctg cgcaactgct 180
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 tatgattgta gcctttatgc ttggaaatta tattaattta cgtgaaagtt ctacagagcc 360
 aaatgattcc ctatggtttt cacttcaaaa gaaaaatgac accactgaaa tagaaacttt 420
 actcttaaatt acagcaccaa aaattattga tgagcaactg gtgtgtcgtt tatcgaaaac 480
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<210> 141
 <211> 413
 <212> PRT
 <213> Homo sapiens

<400> 141
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 35 40 45
 Gln Lys Lys Asn Asp Thr Thr Glu Ile Glu Thr Leu Leu Leu Asn Thr
 50 55 60
 Ala Pro Lys Ile Ile Asp Glu Gln Leu Val Cys Arg Leu Ser Lys Thr
 65 70 75 80

Asp Ile Phe Ile Ile Cys Arg Asp Asn Lys Ile Tyr Leu Asp Lys Met
 85 90 95
 Ile Thr Arg Asn Leu Lys Leu Arg Phe Tyr Gly His Arg Gln Tyr Leu
 100 105 110
 Glu Cys Glu Val Phe Arg Val Glu Gly Ile Lys Asp Asn Leu Asp Asp
 115 120 125
 Ile Lys Arg Ile Ile Lys Ala Arg Glu His Arg Asn Arg Leu Leu Ala
 130 135 140
 Asp Ile Arg Asp Tyr Arg Pro Tyr Ala Asp Leu Val Ser Glu Ile Arg
 145 150 155 160
 Ile Leu Leu Val Gly Pro Val Gly Ser Gly Lys Ser Ser Phe Phe Asn
 165 170 175
 Ser Val Lys Ser Ile Phe His Gly His Val Thr Gly Gln Ala Val Val
 180 185 190
 Gly Ser Asp Thr Thr Ser Ile Thr Glu Arg Tyr Arg Ile Tyr Ser Val
 195 200 205
 Lys Asp Gly Lys Asn Gly Lys Ser Leu Pro Phe Met Leu Cys Asp Thr
 210 215 220
 Met Gly Leu Asp Gly Ala Glu Gly Ala Gly Leu Cys Met Asp Asp Ile
 225 230 235 240
 Pro His Ile Leu Lys Gly Cys Met Pro Asp Arg Tyr Gln Phe Asn Ser
 245 250 255
 Arg Lys Pro Ile Thr Pro Glu His Ser Thr Phe Ile Thr Ser Pro Ser
 260 265 270
 Leu Lys Asp Arg Ile His Cys Val Ala Tyr Val Leu Asp Ile Asn Ser
 275 280 285
 Ile Asp Asn Leu Tyr Ser Lys Met Leu Ala Lys Val Lys Gln Val His
 290 295 300
 Lys Glu Val Leu Asn Cys Gly Ile Ala Tyr Val Ala Leu Leu Thr Lys
 305 310 315 320
 Val Asp Asp Cys Ser Glu Val Leu Gln Asp Asn Phe Leu Asn Met Ser
 325 330 335
 Arg Ser Met Thr Ser Gln Ser Arg Val Met Asn Val His Lys Met Leu
 340 345 350
 Gly Ile Pro Ile Ser Asn Ile Leu Met Val Gly Asn Tyr Ala Ser Asp
 355 360 365
 Leu Glu Leu Asp Pro Met Lys Asp Ile Leu Ile Leu Ser Ala Leu Arg
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<210> 142

<211> 1032

<212> DNA

<213> Homo sapiens

<400> 142

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 cacgtcggtg ccctacggaa acgcacagga acaaaatgtc agtggcaggt gggagttcaa 420
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150

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<210> 143

<211> 303

<212> PRT

<213> Homo sapiens

<400> 143

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20      25      30
Ala Ala Val Gln Ala Ser Pro Leu Gln Ala Leu Asp Phe Phe Gly Asn
35      40      45
Gly Pro Pro Val Asn Tyr Lys Thr Gly Asn Leu Tyr Leu Arg Gly Pro
50      55      60
Leu Lys Lys Ser Asn Ala Pro Leu Val Asn Val Thr Leu Tyr Tyr Glu
65      70      75      80
Ala Leu Cys Gly Gly Cys Arg Ala Phe Leu Ile Arg Glu Leu Phe Pro
85      90      95
Thr Trp Leu Leu Val Met Glu Ile Leu Asn Val Thr Ser Val Pro Tyr
100     105     110
Gly Asn Ala Gln Glu Gln Asn Val Ser Gly Arg Trp Glu Phe Lys Cys
115     120     125
Gln Leu Gly Glu Glu Glu Cys Lys Phe Asn Lys Val Glu Ala Cys Val
130     135     140
Leu Asp Glu Leu Asp Met Glu Leu Ala Phe Leu Thr Met Ser Gly Met
145     150     155     160
Ala Trp Lys Ser Leu Arg Thr Trp Arg Glu Val Cys His Tyr Ala Cys
165     170     175
Ser Ser Thr Pro Gln Gly Cys Arg Gln Asn Tyr His Gly Val Cys Asn
180     185     190
Gly Gly Pro Arg His Ala Ala His Ala Arg Gln Arg Pro Ala Asp Arg
195     200     205
Cys Ser Pro Ala Thr Ala Arg Val Cys Ala Leu Gly His Arg Gln Trp
210     215     220
Glu Thr Leu Gly Arg Ser Asp Pro Ala Pro Tyr Pro Cys Leu Pro Val
225     230     235     240
Val Pro Gly Gln Glu Ala Gly Cys Leu Pro Phe Leu Asn Gln Leu Pro
245     250     255
Pro Glu Cys Leu Leu Arg Val Leu Ala Gly Gly Leu Arg Arg Ala His
260     265     270
Gly Arg Arg Val Gly Thr Arg Leu Pro Ala Phe Phe Ser Asp Pro Asp
275     280     285
Pro Arg His Leu Leu Leu Thr Asn Trp Lys Ile Leu Cys Ile Pro
290     295     300

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<210> 144

<211> 1356
 <212> DNA
 <213> Homo sapiens

<400> 144

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<210> 145
 <211> 180
 <212> PRT
 <213> Homo sapiens

<400> 145

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20          25          30
Cys Gly Gly Glu Leu Val Asp Thr Leu Gln Phe Val Cys Gly Asp Arg
35          40          45
Gly Phe Tyr Phe Ser Arg Pro Ala Ser Arg Val Ser Arg Arg Ser Arg
50          55          60
Gly Ile Val Glu Glu Cys Cys Phe Arg Ser Cys Asp Leu Ala Leu Leu
65          70          75          80
Glu Thr Tyr Cys Ala Thr Pro Ala Lys Ser Glu Arg Asp Val Ser Thr
85          90          95
Pro Pro Thr Val Leu Pro Asp Asn Phe Pro Arg Tyr Pro Val Gly Lys
100         105         110
Phe Phe Gln Tyr Asp Thr Trp Lys Gln Ser Thr Gln Arg Leu Arg Arg
115         120         125
Gly Leu Pro Ala Leu Leu Arg Ala Arg Arg Gly His Val Leu Ala Lys
130         135         140
Glu Leu Glu Ala Phe Arg Glu Ala Lys Arg His Arg Pro Leu Ile Ala
145         150         155         160
Leu Pro Thr Gln Asp Pro Ala His Gly Gly Ala Pro Pro Glu Met Ala
165         170         175
Ser Asn Arg Lys

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180

<210> 146
 <211> 3667
 <212> DNA
 <213> Homo sapiens

<400> 146
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 aaatatgagg gaagttttatt gtgttcttac tttaaatagt ttgcagtttt atttgtgtata 180
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 aagcaactca acggaggagg cgaggagcgc cgggtaccgg gccgggggag ccgcgggctc 420
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<210> 147

<211> 556

<212> PRT

<213> Homo sapiens

<400> 147

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Gln Val Leu Leu Lys Ser Gly Tyr Ala Phe Val Asp Tyr Pro Asp Gln
35          40          45
Asn Trp Ala Ile Arg Ala Ile Glu Thr Leu Ser Gly Lys Val Glu Leu
50          55          60
His Gly Lys Ile Met Glu Val Asp Tyr Ser Val Ser Lys Lys Leu Arg
65          70          75          80
Ser Arg Lys Ile Gln Ile Arg Asn Ile Pro Pro His Leu Gln Trp Glu
85          90          95
Val Leu Asp Gly Leu Leu Ala Gln Tyr Gly Thr Val Glu Asn Val Glu
100          105          110
Gln Val Asn Thr Asp Thr Glu Thr Ala Val Val Asn Val Thr Tyr Ala
115          120          125
Thr Arg Glu Glu Ala Lys Ile Ala Met Glu Lys Leu Ser Gly His Gln
130          135          140
Phe Glu Asn Tyr Ser Phe Lys Ile Ser Tyr Ile Pro Asp Glu Glu Val
145          150          155          160
Ser Ser Pro Ser Pro Pro Gln Arg Ala Gln Arg Gly Asp His Ser Ser
165          170          175
Arg Glu Gln Gly His Ala Pro Gly Gly Thr Ser Gln Ala Arg Gln Ile
180          185          190
Asp Phe Pro Leu Arg Ile Leu Val Pro Thr Gln Phe Val Gly Ala Ile
195          200          205
Ile Gly Lys Glu Gly Leu Thr Ile Lys Asn Ile Thr Lys Gln Thr Gln
210          215          220
Ser Arg Val Asp Ile His Arg Lys Glu Asn Ser Gly Ala Ala Glu Lys
225          230          235          240
Pro Val Thr Ile His Ala Thr Pro Glu Gly Thr Ser Glu Ala Cys Arg
245          250          255
Met Ile Leu Glu Ile Met Gln Lys Glu Ala Asp Glu Thr Lys Leu Ala
260          265          270
Glu Glu Ile Pro Leu Lys Ile Leu Ala His Asn Gly Leu Val Gly Arg
275          280          285
Leu Ile Gly Lys Glu Gly Arg Asn Leu Lys Lys Ile Glu His Glu Thr
290          295          300

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Gly Thr Lys Ile Thr Ile Ser Ser Leu Gln Asp Leu Ser Ile Tyr Asn
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 Pro Glu Arg Thr Ile Thr Val Lys Gly Thr Val Glu Ala Cys Ala Ser
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 Ala Glu Ile Glu Ile Met Lys Lys Leu Arg Glu Ala Phe Glu Asn Asp
 340 345 350
 Met Leu Ala Val Asn Thr His Ser Gly Tyr Phe Ser Ser Leu Tyr Pro
 355 360 365
 His His Gln Phe Gly Pro Phe Pro His His His Ser Tyr Pro Glu Gln
 370 375 380
 Glu Ile Val Asn Leu Phe Ile Pro Thr Gln Ala Val Gly Ala Ile Ile
 385 390 395 400
 Gly Lys Lys Gly Ala His Ile Lys Gln Leu Ala Arg Phe Ala Gly Ala
 405 410 415
 Ser Ile Lys Ile Ala Pro Ala Glu Gly Pro Asp Val Ser Glu Arg Met
 420 425 430
 Val Ile Ile Thr Gly Pro Pro Glu Ala Gln Phe Lys Ala Gln Gly Arg
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 Ile Phe Gly Lys Leu Lys Glu Glu Asn Phe Phe Asn Pro Lys Glu Glu
 450 455 460
 Val Lys Leu Glu Ala His Ile Arg Val Pro Ser Ser Thr Ala Gly Arg
 465 470 475 480
 Val Ile Gly Lys Gly Lys Thr Val Asn Glu Leu Gln Asn Leu Thr
 485 490 495
 Ser Ala Glu Val Ile Val Pro Arg Asp Gln Thr Pro Asp Glu Asn Glu
 500 505 510
 Glu Val Ile Val Arg Ile Ile Gly His Phe Phe Ala Ser Gln Thr Ala
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 Gln Arg Lys Ile Arg Glu Ile Val Gln Gln Val Lys Gln Gln Glu Gln
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 Lys Tyr Pro Gln Gly Val Ala Ser Gln Arg Ser Lys
 545 550 555

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 <211> 1475
 <212> DNA
 <213> Homo sapiens

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 caagtccacag cgccttgac gtctagttct gggatgcac accatggcat atgtgtgggg 300
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<210> 149

<211> 403

<212> PRT

<213> Homo sapiens

<400> 149

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Pro Asp Phe Tyr Asn Asp Trp Met Phe Ile Ala Lys His Leu Pro Asp
          35           40           45
Leu Ile Glu Ser Gly Gln Leu Arg Glu Arg Val Glu Lys Leu Asn Met
          50           55           60
Leu Ser Ile Asp His Leu Thr Asp His Lys Ser Gln Arg Leu Ala Arg
          65           70           75           80
Leu Val Leu Gly Cys Ile Thr Met Ala Tyr Val Trp Gly Lys Gly His
          85           90           95
Gly Asp Val Arg Lys Val Leu Pro Arg Asn Ile Ala Val Pro Tyr Cys
          100          105          110
Gln Leu Ser Lys Lys Leu Glu Leu Pro Pro Ile Leu Val Tyr Ala Asp
          115          120          125
Cys Val Leu Ala Asn Trp Lys Lys Lys Asp Pro Asn Lys Pro Leu Thr
          130          135          140
Tyr Glu Asn Met Asp Val Leu Phe Ser Phe Arg Asp Gly Asp Cys Ser
          145          150          155          160
Lys Gly Phe Phe Leu Val Ser Leu Leu Val Glu Ile Ala Ala Ala Ser
          165          170          175
Ala Ile Lys Val Ile Pro Thr Val Phe Lys Ala Met Gln Met Gln Glu
          180          185          190
Arg Asp Thr Leu Leu Lys Ala Leu Leu Glu Ile Ala Ser Cys Leu Glu
          195          200          205
Lys Ala Leu Gln Val Phe His Gln Ile His Asp His Val Asn Pro Lys
          210          215          220
Ala Phe Phe Ser Val Leu Arg Ile Tyr Leu Ser Gly Trp Lys Gly Asn
          225          230          235          240
Pro Gln Leu Ser Asp Gly Leu Val Tyr Glu Gly Phe Trp Glu Asp Pro
          245          250          255
Lys Glu Phe Ala Gly Gly Ser Ala Gly Gln Ser Ser Val Phe Gln Cys
          260          265          270
Phe Asp Val Leu Leu Gly Ile Gln Gln Thr Ala Gly Gly Gly His Ala
          275          280          285
Ala Gln Phe Leu Gln Asp Met Arg Arg Tyr Met Pro Pro Ala His Arg
          290          295          300
Asn Phe Leu Cys Ser Leu Glu Ser Asn Pro Ser Val Arg Glu Phe Val
          305          310          315          320
Leu Ser Lys Gly Asp Ala Gly Leu Arg Glu Ala Tyr Asp Ala Cys Val
          325          330          335
Lys Ala Leu Val Ser Leu Arg Ser Tyr His Leu Gln Ile Val Thr Lys
          340          345          350

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Tyr Ile Leu Ile Pro Ala Ser Gln Gln Pro Lys Glu Asn Lys Thr Ser
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 385 390 395 400
 Lys Glu Gly

<210> 150
 <211> 2129
 <212> DNA
 <213> Homo sapiens

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<210> 151
 <211> 465
 <212> PRT
 <213> Homo sapiens

<400> 151

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			20					25					30		
Gly	Thr	Ser	Thr	Leu	Ala	Leu	Gln	Leu	Gly	Gln	Arg	Leu	Gly	Gly	Glu
			35				40					45			
Ile	Val	Ser	Ala	Asp	Ser	Met	Gln	Val	Tyr	Glu	Gly	Leu	Asp	Ile	Ile
	50					55					60				
Thr	Asn	Lys	Val	Ser	Ala	Gln	Glu	Gln	Arg	Ile	Cys	Arg	His	His	Met
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Ile	Ser	Phe	Val	Asp	Pro	Leu	Val	Thr	Asn	Tyr	Thr	Val	Val	Asp	Phe
				85					90					95	
Arg	Asn	Arg	Ala	Thr	Ala	Leu	Ile	Glu	Asp	Ile	Phe	Ala	Arg	Asp	Lys
			100					105					110		
Ile	Pro	Ile	Val	Val	Gly	Gly	Thr	Asn	Tyr	Tyr	Ile	Glu	Ser	Leu	Leu
		115					120					125			
Trp	Lys	Val	Leu	Val	Asn	Thr	Lys	Pro	Gln	Glu	Met	Gly	Thr	Glu	Lys
	130					135					140				
Val	Ile	Asp	Arg	Lys	Val	Glu	Leu	Glu	Lys	Glu	Asp	Gly	Leu	Val	Leu
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His	Lys	Arg	Leu	Ser	Gln	Val	Asp	Pro	Glu	Met	Ala	Ala	Lys	Leu	His
				165					170					175	
Pro	His	Asp	Lys	Arg	Lys	Val	Ala	Arg	Ser	Leu	Gln	Val	Phe	Glu	Glu
			180					185					190		
Thr	Gly	Ile	Ser	His	Ser	Glu	Phe	Leu	His	Arg	Gln	His	Thr	Glu	Glu
		195					200					205			
Gly	Gly	Gly	Pro	Leu	Gly	Gly	Pro	Leu	Lys	Phe	Ser	Asn	Pro	Cys	Ile
	210					215					220				
Leu	Trp	Leu	His	Ala	Asp	Gln	Ala	Val	Leu	Asp	Glu	Arg	Leu	Asp	Lys
225					230					235					240
Arg	Val	Asp	Asp	Met	Leu	Ala	Ala	Gly	Leu	Leu	Glu	Glu	Leu	Arg	Asp
				245					250					255	
Phe	His	Arg	Arg	Tyr	Asn	Gln	Lys	Asn	Val	Ser	Glu	Asn	Ser	Gln	Asp
			260					265					270		
Tyr	Gln	His	Gly	Ile	Phe	Gln	Ser	Ile	Gly	Phe	Lys	Glu	Phe	His	Glu
		275					280					285			
Tyr	Leu	Ile	Thr	Glu	Gly	Lys	Cys	Thr	Leu	Glu	Thr	Ser	Asn	Gln	Leu
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Leu	Lys	Lys	Gly	Ile	Glu	Ala	Leu	Lys	Gln	Val	Thr	Lys	Arg	Tyr	Ala
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Arg	Lys	Gln	Asn	Arg	Trp	Val	Lys	Asn	Arg	Phe	Leu	Ser	Arg	Pro	Gly
				325					330					335	
Pro	Ile	Val	Pro	Pro	Val	Tyr	Gly	Leu	Glu	Val	Ser	Asp	Val	Ser	Lys
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Ile	Gln	Gly	His	Lys	Pro	Thr	Ala	Thr	Pro	Ile	Lys	Met	Pro	Tyr	Asn
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Glu	Ala	Glu	Asn	Lys	Arg	Ser	Tyr	His	Leu	Cys	Asp	Leu	Cys	Asp	Arg
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Ile	Ile	Ile	Gly	Asp	Arg	Glu	Trp	Ala	Ala	His	Ile	Lys	Ser	Lys	Ser
				405					410					415	
His	Leu	Asn	Gln	Leu	Lys	Lys	Arg	Arg	Arg	Leu	Asp	Ser	Asp	Ala	Val
			420					425					430		
Asn	Thr	Ile	Glu	Ser	Gln	Ser	Val	Ser	Pro	Asp	His	Asn	Lys	Glu	Pro
		435					440					445			
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450 455 460

Val
465

<210> 152
<211> 2129
<212> DNA
<213> Homo sapiens

<400> 152

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<210> 153
<211> 467
<212> PRT
<213> Homo sapiens

<400> 153

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 Asp Lys Arg Val Asp Asp Met Leu Ala Ala Gly Leu Leu Glu Glu Leu
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 His Glu Tyr Leu Ile Thr Glu Gly Lys Cys Thr Leu Glu Thr Ser Asn
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 Gln Leu Leu Lys Lys Gly Ile Glu Ala Leu Lys Gln Val Thr Lys Arg
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 Tyr Ala Arg Lys Gln Asn Arg Trp Val Lys Asn Arg Phe Leu Ser Arg
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 385 390 395 400
 Asp Arg Ile Ile Ile Gly Asp Arg Glu Trp Ala Ala His Ile Lys Ser
 405 410 415
 Lys Ser His Leu Asn Gln Leu Lys Lys Arg Arg Arg Leu Asp Ser Asp
 420 425 430
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<210> 154
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 <212> DNA
 <213> Homo sapiens

<400> 154

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<210> 155

<211> 1066

<212> PRT

<213> Homo sapiens

<400> 155

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      35          40          45
Gly Ser Leu Phe Gly Tyr Ser Val Ala Leu His Arg Gln Thr Glu Arg
      50          55          60
Gln Gln Arg Tyr Leu Leu Ala Gly Ala Pro Arg Glu Leu Ala Val
65          70          75          80
Pro Asp Gly Tyr Thr Asn Arg Thr Gly Ala Val Tyr Leu Cys Pro Leu
      85          90          95
Thr Ala His Lys Asp Asp Cys Glu Arg Met Asn Ile Thr Val Lys Asn
      100          105          110
Asp Pro Gly His His Ile Ile Glu Asp Met Trp Leu Gly Val Thr Val
      115          120          125
Ala Ser Gln Gly Pro Ala Gly Arg Val Leu Val Cys Ala His Arg Tyr
      130          135          140
Thr Gln Val Leu Trp Ser Gly Ser Glu Asp Gln Arg Arg Met Val Gly
145          150          155          160
Lys Cys Tyr Val Arg Gly Asn Asp Leu Glu Leu Asp Ser Ser Asp Asp
      165          170          175
Trp Gln Thr Tyr His Asn Glu Met Cys Asn Ser Asn Thr Asp Tyr Leu
      180          185          190
Glu Thr Gly Met Cys Gln Leu Gly Thr Ser Gly Gly Phe Thr Gln Asn
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Thr Val Tyr Phe Gly Ala Pro Gly Ala Tyr Asn Trp Lys Gly Asn Ser
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			260					265					270		
Pro	Arg	His	Arg	His	Met	Gly	Ala	Val	Phe	Leu	Leu	Ser	Gln	Glu	Ala
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Gly	Gly	Asp	Leu	Arg	Arg	Arg	Gln	Val	Leu	Glu	Gly	Ser	Gln	Val	Gly
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Ala	Tyr	Phe	Gly	Ser	Ala	Ile	Ala	Leu	Ala	Asp	Leu	Asn	Asn	Asp	Gly
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Trp	Gln	Asp	Leu	Leu	Val	Gly	Ala	Pro	Tyr	Tyr	Phe	Glu	Arg	Lys	Glu
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Glu	Val	Gly	Gly	Ala	Ile	Tyr	Val	Phe	Met	Asn	Gln	Ala	Gly	Thr	Ser
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Phe	Pro	Ala	His	Pro	Ser	Leu	Leu	Leu	His	Gly	Pro	Ser	Gly	Ser	Ala
		355					360					365			
Phe	Gly	Leu	Ser	Val	Ala	Ser	Ile	Gly	Asp	Ile	Asn	Gln	Asp	Gly	Phe
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Gln	Asp	Ile	Ala	Val	Gly	Ala	Pro	Phe	Glu	Gly	Leu	Gly	Lys	Val	Tyr
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Ile	Tyr	His	Ser	Ser	Ser	Lys	Gly	Leu	Leu	Arg	Gln	Pro	Gln	Gln	Val
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Ile	His	Gly	Glu	Lys	Leu	Gly	Leu	Pro	Gly	Leu	Ala	Thr	Phe	Gly	Tyr
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Ser	Leu	Ser	Gly	Gln	Met	Asp	Val	Asp	Glu	Asn	Phe	Tyr	Pro	Asp	Leu
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Leu	Val	Gly	Ser	Leu	Ser	Asp	His	Ile	Val	Leu	Leu	Arg	Ala	Arg	Pro
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Val	Ile	Asn	Ile	Val	His	Lys	Thr	Leu	Val	Pro	Arg	Pro	Ala	Val	Leu
465					470					475					480
Asp	Pro	Ala	Leu	Cys	Thr	Ala	Thr	Ser	Cys	Val	Gln	Val	Glu	Leu	Cys
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Phe	Ala	Tyr	Asn	Gln	Ser	Ala	Gly	Asn	Pro	Asn	Tyr	Arg	Arg	Asn	Ile
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Thr	Leu	Ala	Tyr	Thr	Leu	Glu	Ala	Asp	Arg	Asp	Arg	Arg	Pro	Pro	Arg
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Leu	Arg	Phe	Ala	Gly	Ser	Glu	Ser	Ala	Val	Phe	His	Gly	Phe	Phe	Ser
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Met	Pro	Glu	Met	Arg	Cys	Gln	Lys	Leu	Glu	Leu	Leu	Leu	Met	Asp	Asn
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Leu	Arg	Asp	Lys	Leu	Arg	Pro	Ile	Ile	Ile	Ser	Met	Asn	Tyr	Ser	Leu
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Pro	Leu	Arg	Met	Pro	Asp	Arg	Pro	Arg	Leu	Gly	Leu	Arg	Ser	Leu	Asp
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Ala	Tyr	Pro	Ile	Leu	Asn	Gln	Ala	Gln	Ala	Leu	Glu	Asn	His	Thr	Glu
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Arg	Leu	Gln	Tyr	Ser	Arg	Asp	Val	Arg	Lys	Leu	Leu	Leu	Ser	Ile	Asn
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Val	Thr	Asn	Thr	Arg	Thr	Ser	Glu	Arg	Ser	Gly	Glu	Asp	Ala	His	Glu
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Ala	Leu	Leu	Thr	Leu	Val	Val	Pro	Pro	Ala	Leu	Leu	Leu	Ser	Ser	Val
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163

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 Glu Val Ile Gly Val Thr Leu His Thr Arg Asp Leu Gln Val Gln Leu
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 Gln Leu Ser Thr Ser Ser His Gln Asp Asn Leu Trp Pro Met Ile Leu
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 Thr Leu Leu Val Asp Tyr Thr Leu Gln Thr Ser Leu Ser Met Val Asn
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 His Arg Leu Gln Ser Phe Phe Gly Gly Thr Val Met Gly Glu Ser Gly
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 Met Lys Thr Val Glu Asp Val Gly Ser Pro Leu Lys Tyr Glu Phe Gln
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 Gly Gly Gln Gly Pro Pro Pro Val Thr Leu Ala Ala Ala Lys Lys Ala
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 980 985 990
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<211> 8747

<212> DNA

<213> Homo sapiens

<400> 156

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<210> 157

<211> 769

<212> PRT

<213> Homo sapiens

<400> 157

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Phe Ser Leu Val Leu Gly Leu Gly Gln Gly Glu Asp Asn Arg Cys Ala
35          40          45
Ser Ser Asn Ala Ala Ser Cys Ala Arg Cys Leu Ala Leu Gly Pro Glu
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65          70          75          80
Glu Arg Cys Asp Ile Val Ser Asn Leu Ile Ser Lys Gly Cys Ser Val
85          90          95
Asp Ser Ile Glu Tyr Pro Ser Val His Val Ile Ile Pro Thr Glu Asn
100         105         110
Glu Ile Asn Thr Gln Val Thr Pro Gly Glu Val Ser Ile Gln Leu Arg
115         120         125
Pro Gly Ala Glu Ala Asn Phe Met Leu Lys Val His Pro Leu Lys Lys
130         135         140
Tyr Pro Val Asp Leu Tyr Tyr Leu Val Asp Val Ser Ala Ser Met His
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<210> 158
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<400> 158

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<210> 159

<211> 624

<212> PRT

<213> Homo sapiens

<400> 159

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Ser Glu Lys Thr His Pro Lys Asp Tyr Pro Arg Arg Ala Asn His Trp
      35           40           45
Ser Ala Ile Ile Gly Gly Ser His Ser Lys Asn Tyr Val Leu Trp Glu
      50           55           60
Tyr Gly Gly Tyr Ala Ser Glu Gly Val Lys Gln Val Ala Glu Leu Gly
      65           70           75           80
Ser Pro Val Lys Met Glu Glu Glu Ile Arg Gln Gln Ser Asp Glu Val
      85           90           95
Leu Thr Val Ile Lys Ala Lys Ala Gln Trp Pro Ala Trp Gln Pro Leu
      100          105          110
Asn Val Arg Ala Ala Pro Ser Ala Glu Phe Ser Val Asp Arg Thr Arg
      115          120          125
His Leu Met Ser Phe Leu Thr Met Met Gly Pro Ser Pro Asp Trp Asn

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	195	200
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225	230	235
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<210> 165

<211> 421

<212> PRT

<213> Homo sapiens

<400> 165

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His Thr Val Gly Cys Asp Tyr Cys Gly Pro Leu Val Glu Ile Ala Arg
          35           40           45
Asn Arg Gly Cys Glu Ala Met Val Cys Asp Asn Leu Asn Leu Pro Phe
          50           55           60
Arg Asp Glu Gly Phe Asp Ala Ile Ile Ser Ile Gly Val Ile His His
65          70          75          80
Phe Ser Thr Lys Gln Arg Arg Ile Arg Ala Ile Lys Glu Met Ala Arg
          85          90          95
Val Leu Val Pro Gly Gly Gln Leu Met Ile Tyr Val Trp Ala Met Glu
          100         105         110
Gln Lys Asn Arg Arg Phe Glu Lys Gln Asp Val Leu Val Pro Trp Asn
          115         120         125
Arg Ala Leu Cys Ser Gln Leu Phe Ser Glu Ser Ser Gln Ser Gly Arg
          130         135         140
Lys Arg Gln Cys Gly Tyr Pro Glu Arg Gly His Pro Tyr His Pro Pro
145         150         155         160
Cys Ser Glu Cys Ser Cys Ser Val Cys Phe Lys Glu Gln Gly Gly Ser
          165         170         175
Lys Arg Ser His Ser Val Gly Tyr Glu Pro Ala Met Ala Arg Thr Cys
          180         185         190
Phe Ala Asn Ile Ser Lys Glu Gly Glu Glu Glu Tyr Gly Phe Tyr Ser
          195         200         205

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Thr Leu Gly Lys Ser Phe Arg Ser Trp Phe Phe Ser Arg Ser Leu Asp
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 Glu Ser Thr Leu Arg Lys Gln Ile Glu Arg Val Arg Pro Leu Lys Asn
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 Thr Glu Val Trp Ala Ser Ser Thr Val Thr Val Gln Pro Ser Arg His
 245 250 255
 Ser Ser Leu Asp Phe Asp His Gln Glu Pro Phe Ser Thr Lys Glu Gln
 260 265 270
 Ser Leu Asp Glu Glu Val Phe Val Glu Ser Ser Ser Gly Lys His Leu
 275 280 285
 Glu Trp Leu Arg Ala Pro Gly Thr Leu Lys His Leu Asn Gly Asp His
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 Gln Gly Glu Met Arg Arg Asn Gly Gly Gly Asn Phe Leu Asp Ser Thr
 305 310 315 320
 Asn Thr Gly Val Asn Cys Val Asp Ala Gly Asn Ile Glu Asp Asp Asn
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 Pro Ser Ala Ser Lys Ile Leu Arg Arg Ile Ser Ala Val Asp Ser Thr
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 Asp Phe Asn Pro Asp Asp Thr Met Ser Val Glu Asp Pro Gln Thr Asp
 355 360 365
 Val Leu Asp Ser Thr Ala Phe Met Arg Tyr Tyr His Val Phe Arg Glu
 370 375 380
 Gly Glu Leu Cys Ser Leu Leu Lys Glu Asn Val Ser Glu Leu Arg Ile
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 Leu Ser Ser Gly Asn Asp His Gly Asn Trp Cys Ile Ile Ala Glu Lys
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 Lys Gly Gly Cys Asp
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<210> 166

<211> 1454

<212> DNA

<213> Homo sapiens

<400> 166

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180

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<210> 167

<211> 276

<212> PRT

<213> Homo sapiens

<400> 167

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 Ala Ala Leu Leu Pro Gln Asn Asp Thr Arg Leu Asp Pro Glu Ala Tyr
 35 40 45
 Gly Ala Pro Cys Ala Arg Gly Ser Gln Pro Trp Gln Val Ser Leu Phe
 50 55 60
 Asn Gly Leu Ser Phe His Cys Ala Gly Val Leu Val Asp Gln Ser Trp
 65 70 75 80
 Val Leu Thr Ala Ala His Cys Gly Asn Lys Pro Leu Trp Ala Arg Val
 85 90 95
 Gly Asp Asp His Leu Leu Leu Leu Gln Gly Glu Gln Leu Arg Arg Thr
 100 105 110
 Thr Arg Ser Val Val His Pro Lys Tyr His Gln Gly Ser Gly Pro Ile
 115 120 125
 Leu Pro Arg Arg Thr Asp Glu His Asp Leu Met Leu Leu Lys Leu Ala
 130 135 140
 Arg Pro Val Val Pro Gly Pro Arg Val Arg Ala Leu Gln Leu Pro Tyr
 145 150 155 160
 Arg Cys Ala Gln Pro Gly Asp Gln Cys Gln Val Ala Gly Trp Gly Thr
 165 170 175
 Thr Ala Ala Arg Arg Val Lys Tyr Asn Lys Gly Leu Thr Cys Ser Ser
 180 185 190
 Ile Thr Ile Leu Ser Pro Lys Glu Cys Glu Val Phe Tyr Pro Gly Val
 195 200 205
 Val Thr Asn Asn Met Ile Cys Ala Gly Leu Asp Arg Gly Gln Asp Pro
 210 215 220
 Cys Gln Ser Asp Ser Gly Gly Pro Leu Val Cys Asp Glu Thr Leu Gln
 225 230 235 240
 Gly Ile Leu Ser Trp Gly Val Tyr Pro Cys Gly Ser Ala Gln His Pro
 245 250 255
 Ala Val Tyr Thr Gln Ile Cys Lys Tyr Met Ser Trp Ile Asn Lys Val
 260 265 270
 Ile Arg Ser Asn
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<210> 168

<211> 1506

<212> DNA

<213> Homo sapiens

<400> 168

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<210> 169

<211> 244

<212> PRT

<213> Homo sapiens

<400> 169

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His Pro Tyr Gln Ala Ala Leu Tyr Thr Ser Gly His Leu Leu Cys Gly
          35          40          45
Gly Val Leu Ile His Pro Leu Trp Val Leu Thr Ala Ala His Cys Lys
          50          55          60
Lys Pro Asn Leu Gln Val Phe Leu Gly Lys His Asn Leu Arg Gln Arg
65          70          75          80
Glu Ser Ser Gln Glu Gln Ser Ser Val Val Arg Ala Val Ile His Pro
          85          90          95
Asp Tyr Asp Ala Ala Ser His Asp Gln Asp Ile Met Leu Leu Arg Leu
          100         105         110
Ala Arg Pro Ala Lys Leu Ser Glu Leu Ile Gln Pro Leu Pro Leu Glu
          115         120         125
Arg Asp Cys Ser Ala Asn Thr Thr Ser Cys His Ile Leu Gly Trp Gly
          130         135         140
Lys Thr Ala Asp Gly Asp Phe Pro Asp Thr Ile Gln Cys Ala Tyr Ile
          145         150         155         160
His Leu Val Ser Arg Glu Glu Cys Glu His Ala Tyr Pro Gly Gln Ile
          165         170         175
Thr Gln Asn Met Leu Cys Ala Gly Asp Glu Lys Tyr Gly Lys Asp Ser
          180         185         190
Cys Gln Gly Asp Ser Gly Gly Pro Leu Val Cys Gly Asp His Leu Arg
          195         200         205
Gly Leu Val Ser Trp Gly Asn Ile Pro Cys Gly Ser Lys Glu Lys Pro
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225
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230

235

240

<210> 170
<211> 1641
<212> DNA
<213> Homo sapiens

<400> 170
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<210> 171
<211> 469
<212> PRT
<213> Homo sapiens

<400> 171
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Gly Leu Gly Ser Ser Ser Leu Tyr Gly Leu Gly Ala Ser Arg Pro Arg
35 40 45
Val Ala Val Arg Ser Ala Tyr Gly Gly Pro Val Gly Ala Gly Ile Arg
50 55 60
Glu Val Thr Ile Asn Gln Ser Leu Leu Ala Pro Leu Arg Leu Asp Ala
65 70 75 80
Asp Pro Ser Leu Gln Arg Val Arg Gln Glu Ser Glu Gln Ile Lys
85 90 95

183

Ala Leu Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu
 100 105 110
 Glu Gln Gln Asn Lys Leu Leu Glu Thr Lys Trp Thr Leu Leu Gln Glu
 115 120 125
 Gln Lys Ser Ala Lys Ser Ser Arg Leu Pro Asp Ile Phe Glu Ala Gln
 130 135 140
 Ile Ala Gly Leu Arg Gly Gln Leu Glu Ala Leu Gln Val Asp Gly Gly
 145 150 155 160
 Arg Leu Glu Gln Gly Leu Arg Thr Met Gln Asp Val Val Glu Asp Phe
 165 170 175
 Lys Asn Lys Tyr Glu Asp Glu Ile Asn Arg Arg Thr Ala Ala Glu Asn
 180 185 190
 Glu Phe Val Val Leu Lys Lys Asp Val Asp Ala Ala Tyr Met Ser Lys
 195 200 205
 Val Glu Leu Glu Ala Lys Val Asp Ala Leu Asn Asp Glu Ile Asn Phe
 210 215 220
 Leu Arg Thr Leu Asn Glu Thr Glu Leu Thr Glu Leu Gln Ser Gln Ile
 225 230 235 240
 Ser Asp Thr Ser Val Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp
 245 250 255
 Leu Asp Gly Ile Ile Ala Glu Val Lys Ala Gln Tyr Glu Glu Met Ala
 260 265 270
 Lys Cys Ser Arg Ala Glu Ala Glu Ala Trp Tyr Gln Thr Lys Phe Glu
 275 280 285
 Thr Leu Gln Ala Gln Ala Gly Lys His Gly Asp Asp Leu Arg Asn Thr
 290 295 300
 Arg Asn Glu Ile Ser Glu Met Asn Arg Ala Ile Gln Arg Leu Gln Ala
 305 310 315 320
 Glu Ile Asp Asn Ile Lys Asn Gln Arg Ala Lys Leu Glu Ala Ala Ile
 325 330 335
 Ala Glu Ala Glu Glu Cys Gly Glu Leu Ala Leu Lys Asp Ala Arg Ala
 340 345 350
 Lys Gln Glu Glu Leu Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met
 355 360 365
 Ala Arg Gln Leu Arg Glu Tyr Gln Glu Leu Met Ser Val Lys Leu Ala
 370 375 380
 Leu Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu
 385 390 395 400
 Ser Arg Leu Ala Gly Asp Gly Val Gly Ala Val Asn Ile Ser Val Met
 405 410 415
 Asn Ser Thr Gly Gly Ser Ser Ser Gly Gly Gly Ile Gly Leu Thr Leu
 420 425 430
 Gly Gly Thr Met Gly Ser Asn Ala Leu Ser Phe Ser Ser Ser Ala Gly
 435 440 445
 Pro Gly Leu Leu Lys Ala Tyr Ser Ile Arg Thr Ala Ser Ala Ser Arg
 450 455 460
 Arg Ser Ala Arg Asp
 465

<210> 172

<211> 1640

<212> DNA

<213> Homo sapiens

<400> 172

gcgagtgcgc gctcctcctc gcccgccgct aggtccatcc cggcccagcc accatgtcca 60
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aggtgcgcct gagctccgct cgccccggcg gccttggcag cagcagcctc tacggcctcg 180
gcgcctcgcg gccgcgcgtg gccgtgcgct ctgcctatgg gggcccgggtg ggcgccggca 240
tccgcgaggt caccattaac cagagcctgc tggccccgct gcggtggac gccgacccct 300
ccctccagcg ggtgcgccag gaggagagcg agcagatcaa gaccctcaac aacaagtttg 360
cctccttcat cgacaaggtg cggtttcttg agcagcagaa caagctgctg gagaccaagt 420
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acaatcacia gaagattccc acccctgcct cccatgcctg gtcccaagac agtgagacag 1560
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<210> 173

<211> 469

<212> PRT

<213> Homo sapiens

<400> 173

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Met Ser Ile His Phe Ser Ser Pro Val Phe Thr Ser Arg Ser Ala Ala
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      20           25           30
Gly Leu Gly Ser Ser Ser Leu Tyr Gly Leu Gly Ala Ser Arg Pro Arg
      35           40           45
Val Ala Val Arg Ser Ala Tyr Gly Gly Pro Val Gly Ala Gly Ile Arg
      50           55           60
Glu Val Thr Ile Asn Gln Ser Leu Leu Ala Pro Leu Arg Leu Asp Ala
      65           70           75           80
Asp Pro Ser Leu Gln Arg Val Arg Gln Glu Glu Ser Glu Gln Ile Lys
      85           90           95
Thr Leu Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu
      100          105          110
Glu Gln Gln Asn Lys Leu Leu Glu Thr Lys Trp Thr Leu Leu Gln Glu
      115          120          125
Gln Lys Ser Ala Lys Ser Ser Arg Leu Pro Asp Ile Phe Glu Ala Gln
      130          135          140
Ile Ala Gly Leu Arg Gly Gln Leu Glu Ala Leu Gln Val Asp Gly Gly
      145          150          155          160
Arg Leu Glu Ala Glu Leu Arg Ser Met Gln Asp Val Val Glu Asp Phe
      165          170          175
Lys Asn Lys Tyr Glu Asp Glu Ile Asn Arg Arg Thr Ala Ala Glu Asn
      180          185          190
Glu Phe Val Val Leu Lys Lys Asp Val Asp Ala Ala Tyr Met Ser Lys

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195	200	205
Val Glu Leu Glu Ala Lys	Val Asp Ala Leu Asn	Asp Glu Ile Asn Phe
210	215	220
Leu Arg Thr Leu Asn Glu	Thr Glu Leu Thr Glu	Leu Gln Ser Gln Ile
225	230	235
Ser Asp Thr Ser Val	Leu Ser Met Asp	Asn Ser Arg Ser Leu Asp
245	250	255
Leu Asp Gly Ile Ile Ala	Glu Val Lys Ala Gln	Tyr Glu Glu Met Ala
260	265	270
Lys Cys Ser Arg Ala Glu	Ala Glu Ala Trp Tyr	Gln Thr Lys Phe Glu
275	280	285
Thr Leu Gln Ala Gln Ala	Gly Lys His Gly Asp	Asp Leu Arg Asn Thr
290	295	300
Arg Asn Glu Ile Ser Glu	Met Asn Arg Ala Ile	Gln Arg Leu Gln Ala
305	310	315
Glu Ile Asp Asn Ile Lys	Asn Gln Arg Ala Lys	Leu Glu Ala Ala Ile
325	330	335
Ala Glu Ala Glu Glu Arg	Gly Glu Leu Ala Leu	Lys Asp Ala Arg Ala
340	345	350
Lys Gln Glu Glu Leu Glu	Ala Ala Leu Gln Arg	Ala Lys Gln Asp Met
355	360	365
Ala Arg Gln Leu Arg Glu	Tyr Gln Glu Leu Met	Ser Val Lys Leu Ala
370	375	380
Leu Asp Ile Glu Ile Ala	Thr Tyr Arg Lys Leu	Leu Glu Gly Glu Glu
385	390	395
Ser Arg Leu Ala Gly Asp	Gly Val Gly Ala Val	Asn Ile Ser Val Met
405	410	415
Asn Ser Thr Gly Gly Ser	Ser Ser Gly Gly Ile	Gly Leu Thr Leu
420	425	430
Gly Gly Thr Met Gly Ser	Asn Ala Leu Ser Phe	Ser Ser Ser Ala Gly
435	440	445
Pro Gly Leu Leu Lys Ala	Tyr Ser Ile Arg Thr	Ala Ser Ala Ser Arg
450	455	460
Arg Ser Ala Arg Asp		
465		

<210> 174
 <211> 2186
 <212> DNA
 <213> Homo sapiens

<400> 174
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 gtccgccgag ggcgcaccac cggcccgtct cgcccgcgc gccggggagg tggagcacga 180
 gcgcacgtgt taggaccgca aagatggtga actatgctg ggcagggcga agccagagga 240
 aactctggtg gaggtccgta gcggtcctga cgtgcaaatc ggtcgtccga cctgggtata 300
 ggggcgggct ccaggcgagg cggtcgacgc tcctgaaaac ttgcgcgcgc gctcgcgcca 360
 ctgcgcccgg agcgatgaag atggtcgcg cctggacgcg gttctactcc aacagctgct 420
 gcttgtgctg ccatgtccgc accggcacca tcctgctcgg cgtctggtat ctgatcatca 480
 atgctgtggt actggtgatt ttattgagtg ccctggctga tccggatcag tataactttt 540
 caagttctga actgggaggt gactttgagt tcatggatga tgccaacatg tgcattgcca 600
 ttgcgatttc tcttctcatg atcctgatat gtgctatggc tacttacgga gcgtacaagc 660
 aacgcgcagc ctggatcatc ccattcttct gttaccagat ctttgacttt gccctgaaca 720
 tgttggttgc aatcactgtg cttatttatc caaactccat tcaggaatac atacggcaac 780
 tgccctcctaa ttttccctac agagatgatg tcatgtcagt gaatcctacc tgtttggtcc 840
 ttattattct tctgtttatt agcattatct tgacttttaa gggttacttg attagctgtg 900

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tttggaaactg ctaccgatac atcaatggta ggaactcctc tgatgtcctg gtttatgtta 960
ccagcaatga cactacggtg ctgctacccc cgtatgatga tgccactgtg aatgggtgctg 1020
ccaaggagcc accgccacct tacgtgtctg cctaagcctt caagtgggcg gagctgaggg 1080
cagcagcttg actttgcaga catctgagca atagttctgt tatttcactt ttgccatgag 1140
cctctctgag cttgtttgtt gctgaaatgc tacttttttaa aatttagatg ttagattgaa 1200
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cttcagccat tccagcatag agaacaaaac cttatggaaa caggaatgtc aattgtgtaa 1500
tcattgttct aattaggtaa atagaagtc ttatgtatgt gttacaagaa tttccccac 1560
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ctagtcacct tttaaaatgt aaacattttc agaaaaatga ggattgcctt ccttgatgc 2040
gctttttacc ttgactacct gaattgcaag ggatttttat atattcatat gttacaaagt 2100
cagcaactct cctgttggtt cattattgaa tgtgctgtaa attaagttgt ttgcaattaa 2160
aacaaggttt gccacaaaa aaaaaa 2186

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<210> 175

<211> 283

<212> PRT

<213> Homo sapiens

<400> 175

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Met Val Asn Tyr Ala Trp Ala Gly Arg Ser Gln Arg Lys Leu Trp Trp
  1          5          10          15
Arg Ser Val Ala Val Leu Thr Cys Lys Ser Val Val Arg Pro Gly Tyr
      20          25          30
Arg Gly Gly Leu Gln Ala Arg Arg Ser Thr Leu Leu Lys Thr Cys Ala
      35          40          45
Arg Ala Arg Ala Thr Ala Pro Gly Ala Met Lys Met Val Ala Pro Trp
      50          55          60
Thr Arg Phe Tyr Ser Asn Ser Cys Cys Leu Cys Cys His Val Arg Thr
      65          70          75          80
Gly Thr Ile Leu Leu Gly Val Trp Tyr Leu Ile Ile Asn Ala Val Val
      85          90          95
Leu Leu Ile Leu Leu Ser Ala Leu Ala Asp Pro Asp Gln Tyr Asn Phe
      100          105          110
Ser Ser Ser Glu Leu Gly Gly Asp Phe Glu Phe Met Asp Asp Ala Asn
      115          120          125
Met Cys Ile Ala Ile Ala Ile Ser Leu Leu Met Ile Leu Ile Cys Ala
      130          135          140
Met Ala Thr Tyr Gly Ala Tyr Lys Gln Arg Ala Ala Trp Ile Ile Pro
      145          150          155          160
Phe Phe Cys Tyr Gln Ile Phe Asp Phe Ala Leu Asn Met Leu Val Ala
      165          170          175
Ile Thr Val Leu Ile Tyr Pro Asn Ser Ile Gln Glu Tyr Ile Arg Gln
      180          185          190
Leu Pro Pro Asn Phe Pro Tyr Arg Asp Asp Val Met Ser Val Asn Pro
      195          200          205
Thr Cys Leu Val Leu Ile Ile Leu Leu Phe Ile Ser Ile Ile Leu Thr
      210          215          220
Phe Lys Gly Tyr Leu Ile Ser Cys Val Trp Asn Cys Tyr Arg Tyr Ile

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187

225		230		235		240
Asn Gly Arg Asn Ser Ser Asp Val Leu Val Tyr Val Thr Ser Asn Asp						
	245		250		255	
Thr Thr Val Leu Leu Pro Pro Tyr Asp Asp Ala Thr Val Asn Gly Ala						
	260		265		270	
Ala Lys Glu Pro Pro Pro Pro Tyr Val Ser Ala						
	275		280			

<210> 176
 <211> 597
 <212> DNA
 <213> Homo sapiens

<400> 176
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 aacttcagg acaaccaatt ccaggggaag tggatatgtg taggcctggc agggaaatgca 180
 attctcagag aagacaaaga cccgcaaaag atgtatgcca ccatctatga gctgaaagaa 240
 gacaagagct acaatgtcac ctccgtcctg tttaggaaaa agaagtgtga ctactggatc 300
 aggacttttg ttccagggttg ccagcccggc gagttcacgc tgggcaacat taagagttac 360
 cctggattaa cgagttacct cgtccgagtg gtgagcacca actacaacca gcatgctatg 420
 gtgttcttca agaaagtttc tcaaaacagg gagtacttca agatcaccct ctacgggaga 480
 accaaggagc tgacttcgga actaaaggag aacttcatcc gcttctccaa atatctgggc 540
 ctccctgaaa accacatcgt cttccctgtc ccaatcgacc agtgtatcga cggctga 597

<210> 177
 <211> 198
 <212> PRT
 <213> Homo sapiens

<400> 177
 Met Pro Leu Gly Leu Leu Trp Leu Gly Leu Ala Leu Leu Gly Ala Leu
 1 5 10 15
 His Ala Gln Ala Gln Asp Ser Thr Ser Asp Leu Ile Pro Ala Pro Pro
 20 25 30
 Leu Ser Lys Val Pro Leu Gln Gln Asn Phe Gln Asp Asn Gln Phe Gln
 35 40 45
 Gly Lys Trp Tyr Val Val Gly Leu Ala Gly Asn Ala Ile Leu Arg Glu
 50 55 60
 Asp Lys Asp Pro Gln Lys Met Tyr Ala Thr Ile Tyr Glu Leu Lys Glu
 65 70 75 80
 Asp Lys Ser Tyr Asn Val Thr Ser Val Leu Phe Arg Lys Lys Lys Cys
 85 90 95
 Asp Tyr Trp Ile Arg Thr Phe Val Pro Gly Cys Gln Pro Gly Glu Phe
 100 105 110
 Thr Leu Gly Asn Ile Lys Ser Tyr Pro Gly Leu Thr Ser Tyr Leu Val
 115 120 125
 Arg Val Val Ser Thr Asn Tyr Asn Gln His Ala Met Val Phe Phe Lys
 130 135 140
 Lys Val Ser Gln Asn Arg Glu Tyr Phe Lys Ile Thr Leu Tyr Gly Arg
 145 150 155 160
 Thr Lys Glu Leu Thr Ser Glu Leu Lys Glu Asn Phe Ile Arg Phe Ser
 165 170 175
 Lys Tyr Leu Gly Leu Pro Glu Asn His Ile Val Phe Pro Val Pro Ile
 180 185 190
 Asp Gln Cys Ile Asp Gly
 195

<210> 178
 <211> 1518
 <212> DNA
 <213> Homo sapiens

<400> 178
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 gggcagcacc atgcagcccc tgtggctctg ctgggcactc tgggtgttgc ccctggccag 120
 ccccgggggc gccctgaccg gggagcagct cctgggcagc ctgctgcggc agctgcagct 180
 caaagaggtg cccaccctgg acagggccga catggaggag ctggatcatc ccacccacgt 240
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 gttcagccag agcttccgag aggtggccgg caggttcctg gcgttggagg ccagcacaca 360
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 gctgcggctc ttccaggagc cgggtcccaa ggccgcgctg cacaggcacg ggcggctgtc 480
 cccgcgcagc gcccgggccc gggtagccgt cgagtggctg cgcgtccgag acgacggctc 540
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 gctgggtccgc tttgcctcgc agggggcgcc agccgggctt ggggagcccc agctggagct 780
 gcacaccctg gaccttgggg actatggagc tcagggcgac tgtgaccctg aagcaccaat 840
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 ggccgagaac tgggtgctgg agcccccggt cttcctggct tatgagtgtg tgggcacctg 960
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 ctcacctaatt ttttgccttct cagggaatgag aatctttggc cactggagag cccttgctca 1380
 gttttctcta ttcttattat tcaactgcact atattctaag cacttacatg tggagatact 1440
 gtaacctgag ggcagaaagc ccaatgtgtc attgtttact tgtcctgtca ctggatctgg 1500
 gctaaagtcc tccaccac 1518

<210> 179
 <211> 366
 <212> PRT
 <213> Homo sapiens

<400> 179
 Met Gln Pro Leu Trp Leu Cys Trp Ala Leu Trp Val Leu Pro Leu Ala
 1 5 10 15
 Ser Pro Gly Ala Leu Thr Gly Glu Gln Leu Leu Gly Ser Leu Leu
 20 25 30
 Arg Gln Leu Gln Leu Lys Glu Val Pro Thr Leu Asp Arg Ala Asp Met
 35 40 45
 Glu Glu Leu Val Ile Pro Thr His Val Arg Ala Gln Tyr Val Ala Leu
 50 55 60
 Leu Gln Arg Ser His Gly Asp Arg Ser Arg Gly Lys Arg Phe Ser Gln
 65 70 75 80
 Ser Phe Arg Glu Val Ala Gly Arg Phe Leu Ala Leu Glu Ala Ser Thr
 85 90 95
 His Leu Leu Val Phe Gly Met Glu Gln Arg Leu Pro Pro Asn Ser Glu
 100 105 110
 Leu Val Gln Ala Val Leu Arg Leu Phe Gln Glu Pro Val Pro Lys Ala
 115 120 125
 Ala Leu His Arg His Gly Arg Leu Ser Pro Arg Ser Ala Arg Ala Arg

189

130	135	140
Val Thr Val Glu Trp	Leu Arg Val Arg Asp Asp	Gly Ser Asn Arg Thr
145	150	155
Ser Leu Ile Asp	Ser Arg Leu Val Ser Val His	Glu Ser Gly Trp Lys
165	170	175
Ala Phe Asp Val Thr	Glu Ala Val Asn Phe Trp	Gln Gln Leu Ser Arg
180	185	190
Pro Arg Gln Pro Leu	Leu Leu Gln Val Ser Val	Gln Arg Glu His Leu
195	200	205
Gly Pro Leu Ala Ser	Gly Ala His Lys Leu Val	Arg Phe Ala Ser Gln
210	215	220
Gly Ala Pro Ala Gly	Leu Gly Glu Pro Gln Leu	Glu Leu His Thr Leu
225	230	235
Asp Leu Gly Asp Tyr	Gly Ala Gln Gly Asp Cys	Asp Pro Glu Ala Pro
245	250	255
Met Thr Glu Gly Thr	Arg Cys Cys Arg Gln Glu	Met Tyr Ile Asp Leu
260	265	270
Gln Gly Met Lys Trp	Ala Glu Asn Trp Val Leu	Glu Pro Pro Gly Phe
275	280	285
Leu Ala Tyr Glu Cys	Val Gly Thr Cys Arg Gln	Pro Pro Glu Ala Leu
290	295	300
Ala Phe Lys Trp Pro	Phe Leu Gly Pro Arg Gln	Cys Ile Ala Ser Glu
305	310	315
Thr Asp Ser Leu Pro	Met Ile Val Ser Ile Lys	Glu Gly Gly Arg Thr
325	330	335
Arg Pro Gln Val Ser	Leu Pro Asn Met Arg Val	Gln Lys Cys Ser
340	345	350
Cys Ala Ser Asp Gly	Ala Leu Val Pro Arg Arg	Leu Gln Pro
355	360	365

<210> 180
 <211> 444
 <212> DNA
 <213> Homo sapiens

<400> 180
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 aatgccgagt tctgcccagc tcttggtttct gagctgttag acttcttctt cattagttaa 180
 cctctgttca agttaagtct tgccaaattt gatgccctc cggaagctgt tgcagccaag 240
 ttaggagtga agagatgcac ggatcagatg tcccttcaga aacgaagcct cattgcggaa 300
 gtcctgggtga aaatattgaa gaaatgtagt gtgtgacatg taaaaacttt catcctggtt 360
 tccactgtct ttcaatgaca ccctgatctt cactgcagaa tgtaaagggt tcaacgtctt 420
 gctttaataa atcacttgct ctac 444

<210> 181
 <211> 90
 <212> PRT
 <213> Homo sapiens

<400> 181
 Met Lys Leu Ser Val Cys Leu Leu Leu Val Thr Leu Ala Leu Cys Cys
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 Tyr Gln Ala Asn Ala Glu Phe Cys Pro Ala Leu Val Ser Glu Leu Leu
 20 25 30
 Asp Phe Phe Phe Ile Ser Glu Pro Leu Phe Lys Leu Ser Leu Ala Lys
 35 40 45

190

Phe Asp Ala Pro Pro Glu Ala Val Ala Ala Lys Leu Gly Val Lys Arg
 50 55 60
 Cys Thr Asp Gln Met Ser Leu Gln Lys Arg Ser Leu Ile Ala Glu Val
 65 70 75 80
 Leu Val Lys Ile Leu Lys Lys Cys Ser Val
 85 90

<210> 182

<211> 754

<212> DNA

<213> Homo sapiens

<400> 182

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 aggaaagcat aggaggtttg aaatggaccg ggaacctaag agtgccagat actgtgctga 180
 gtgtaatagg ctgcaccttg ctgaggaagg agacttttgg gcagagtcaa gcatgttggg 240
 cctcaagatc acctactttg cactgatgga tggaaagggtg tatgacatca cagagtgggc 300
 tggatgccag cgtgtaggta tctccccaga tacccacaga gtcccctatc acatctcatt 360
 tggttctcgg attccaggca ccagagggcg gcagagagcc accccagatg cccctcctgc 420
 tgatcttcag gatttcttga gtcggatctt tcaagtaccc ccagggcaga tgccaatggg 480
 aacttctttg cagctcctea gcctgccccct ggagccgctg cagcctctaa gcccaacagc 540
 acagtaccca agggagaagc caaacctaag cggcggaaga aagtgaggag gcccttccaa 600
 cgttgatgcc ccttctcttt cctcaaatca atgtcaggga gtcaaaaggg ctgtagcaca 660
 ggatggagtt tgatttatcc ctctctcccc aacacctagg aactgaatct ttttcttttt 720
 attttttgag atggagtctt gctctgttgc ccag 754

<210> 183

<211> 191

<212> PRT

<213> Homo sapiens

<400> 183

Met Lys Arg Met Ala Glu Asn Glu Leu Ser Arg Ser Val Asn Glu Phe
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 Leu Ser Lys Leu Gln Asp Asp Leu Lys Glu Ala Met Asn Thr Met Met
 20 25 30
 Cys Ser Arg Cys Gln Gly Lys His Arg Arg Phe Glu Met Asp Arg Glu
 35 40 45
 Pro Lys Ser Ala Arg Tyr Cys Ala Glu Cys Asn Arg Leu His Pro Ala
 50 55 60
 Glu Glu Gly Asp Phe Trp Ala Glu Ser Ser Met Leu Gly Leu Lys Ile
 65 70 75 80
 Thr Tyr Phe Ala Leu Met Asp Gly Lys Val Tyr Asp Ile Thr Glu Trp
 85 90 95
 Ala Gly Cys Gln Arg Val Gly Ile Ser Pro Asp Thr His Arg Val Pro
 100 105 110
 Tyr His Ile Ser Phe Gly Ser Arg Ile Pro Gly Thr Arg Gly Arg Gln
 115 120 125
 Arg Ala Thr Pro Asp Ala Pro Pro Ala Asp Leu Gln Asp Phe Leu Ser
 130 135 140
 Arg Ile Phe Gln Val Pro Pro Gly Gln Met Pro Met Gly Thr Ser Leu
 145 150 155 160
 Gln Leu Leu Ser Leu Pro Leu Glu Pro Leu Gln Pro Leu Ser Pro Thr
 165 170 175
 Ala Gln Tyr Pro Arg Glu Lys Pro Asn Leu Ser Gly Gly Arg Lys
 180 185 190

<210> 184
 <211> 2511
 <212> DNA
 <213> Homo sapiens

<400> 184
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 tgaaccacgg gcctcctctg cactcgcacg agtaccgcga cacagctcat accaacgcca 240
 tggcccccag catgggctcc tctgtcaatg acgctttaaa gagagataaa gatgccattt 300
 atggacaccc cctcttccct ctcttagcac tgatttttga gaaatgtgaa ttagctactt 360
 gtaccccccg cgagccgggg gtggcggggtc gggacgtctg ctgctcagag tcattcaatg 420
 aagatatagc cgtgttcgcc aaacagattc gcgcagaaaa acctctattt tcttctaata 480
 cagaactgga taacttgatg attcaagcca tacaagtatt aaggtttcat ctattggaat 540
 tagagaaggt acacgaatta tgtgacaatt tctgccaccg gtatattagc tgtttgaaag 600
 ggaaaatgcc tatcgatttg gtgatagacg atagagaagg aggatcaaaa tcagacagtg 660
 aagatataac aagatcagca aatctaactg accagccctc ttggaacaga gatcatgatg 720
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<210> 185
 <211> 390
 <212> PRT
 <213> Homo sapiens

<400> 185
 Met Ala Gln Arg Tyr Asp Asp Leu Pro His Tyr Gly Gly Met Asp Gly

192

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20	25	30	
Met Gln Pro Val His His Leu Asn His Gly Pro Pro Leu His Ser His			
35	40	45	
Gln Tyr Pro His Thr Ala His Thr Asn Ala Met Ala Pro Ser Met Gly			
50	55	60	
Ser Ser Val Asn Asp Ala Leu Lys Arg Asp Lys Asp Ala Ile Tyr Gly			
65	70	75	80
His Pro Leu Phe Pro Leu Leu Ala Leu Ile Phe Glu Lys Cys Glu Leu			
85	90	95	
Ala Thr Cys Thr Pro Arg Glu Pro Gly Val Ala Gly Gly Asp Val Cys			
100	105	110	
Ser Ser Glu Ser Phe Asn Glu Asp Ile Ala Val Phe Ala Lys Gln Ile			
115	120	125	
Arg Ala Glu Lys Pro Leu Phe Ser Ser Asn Pro Glu Leu Asp Asn Leu			
130	135	140	
Met Ile Gln Ala Ile Gln Val Leu Arg Phe His Leu Leu Glu Leu Glu			
145	150	155	160
Lys Val His Glu Leu Cys Asp Asn Phe Cys His Arg Tyr Ile Ser Cys			
165	170	175	
Leu Lys Gly Lys Met Pro Ile Asp Leu Val Ile Asp Asp Arg Glu Gly			
180	185	190	
Gly Ser Lys Ser Asp Ser Glu Asp Ile Thr Arg Ser Ala Asn Leu Thr			
195	200	205	
Asp Gln Pro Ser Trp Asn Arg Asp His Asp Asp Thr Ala Ser Thr Arg			
210	215	220	
Ser Gly Gly Thr Pro Gly Pro Ser Ser Gly Gly His Thr Ser His Ser			
225	230	235	240
Gly Asp Asn Ser Ser Glu Gln Gly Asp Gly Leu Asp Asn Ser Val Ala			
245	250	255	
Ser Pro Ser Thr Gly Asp Asp Asp Asp Pro Asp Lys Asp Lys Lys Arg			
260	265	270	
His Lys Lys Arg Gly Ile Phe Pro Lys Val Ala Thr Asn Ile Met Arg			
275	280	285	
Ala Trp Leu Phe Gln His Leu Thr His Pro Tyr Pro Ser Glu Glu Gln			
290	295	300	
Lys Lys Gln Leu Ala Gln Asp Thr Gly Leu Thr Ile Leu Gln Val Asn			
305	310	315	320
Asn Trp Phe Ile Asn Ala Arg Arg Arg Ile Val Gln Pro Met Ile Asp			
325	330	335	
Gln Ser Asn Arg Ala Val Ser Gln Gly Thr Pro Tyr Asn Pro Asp Gly			
340	345	350	
Gln Pro Met Gly Gly Phe Val Met Asp Gly Gln Gln His Met Gly Ile			
355	360	365	
Arg Ala Pro Gly Pro Met Ser Gly Met Gly Met Asn Met Gly Met Glu			
370	375	380	
Gly Gln Trp His Tyr Met			
385	390		

<210> 186

<211> 517

<212> DNA

<213> Homo sapiens

<400> 186

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acctgaatac aaagagcttc ttcaagagtt catagacagt gatgccgtg cagaggctat 240
ggggaaattc aagcagtgtt tcctcaacca gtcacataga actctgaaaa acttttgact 300
gatgatgcat acagtgtacg acagcatttg gtgtaatatg aagagtaatt aactttaccc 360
aaggcgtttg gctcagaggg ctacagacta tggccagAAC tcactctgtg attgctagaa 420
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<210> 187

<211> 95

<212> PRT

<213> Homo sapiens

<400> 187

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Met Lys Leu Leu Met Val Leu Met Leu Ala Ala Leu Leu Leu His Cys
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Tyr Ala Asp Ser Gly Cys Lys Leu Leu Glu Asp Met Val Glu Lys Thr
          20          25          30
Ile Asn Ser Asp Ile Ser Ile Pro Glu Tyr Lys Glu Leu Leu Gln Glu
          35          40          45
Phe Ile Asp Ser Asp Ala Ala Glu Ala Met Gly Lys Phe Lys Gln
          50          55          60
Cys Phe Leu Asn Gln Ser His Arg Thr Leu Lys Asn Phe Gly Leu Met
          65          70          75          80
Met His Thr Val Tyr Asp Ser Ile Trp Cys Asn Met Lys Ser Asn
          85          90          95

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<210> 188

<211> 2048

<212> DNA

<213> Homo sapiens

<400> 188

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aaaagtggcc ccggacgcgc gagcctgagg attctgcaca aaagagggtg ccaaaatgaa 180
gaccctgatg cgccatgggtc tggcagtgtg tttagcgctc accaccatgt gcaccagctt 240
gttgctagtg tacagcagcc tcggcgcca gaaggagcgg ccccgagcgc agcagcagca 300
gcagcagcaa cagcagcagc aggcgtcggc caccggcagc tcgcagccgg cggcgagag 360
cagcaccag cagcgcccc gggtccccgc gggaccgagg ccactggagc gatacctcgg 420
agtggcggac cacaagcccc tgaaaatgca ctgcaggagc tgtgccctgg tgaccagctc 480
agggcatctg ctgcacagtc ggcaaggctc ccagattgac cagacagagt gtgtcatccg 540
catgaatgac gccccacac gcggctatgg gcgtgacgtg ggcaatcgca ccagcctgag 600
ggtcacgcgc cattccagca tccagaggat cctccgcaac cgccatgacc tgctcaacgt 660
gagccagggc accgtgttca tcttctgggg cccagcagc tacatgcggc gggacggcaa 720
gggcccaggtc tacaacaacc tgcatctcct gagccagggtg ctgccccggc tgaaggcctt 780
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caatcacctc tcagtacctt atcattatta tgaacctttt ggacctgatg aatgtacaat 1020
gtacctctcc catgagcgag gacgcaaggg cagtcacac cgctttatca cagagaaacg 1080
agtctttaag aactgggcac ggacattcaa tattcacttt tttcaaccag actggaaacc 1140
agaatcactt gctataaatc atcctgagaa taaacctgtg ttctaaggaa tgagcatgcc 1200
agactgtaat cccagggtatt cactgcatca gacaccgaga cactgaactt cctgagccac 1260
cagacaggaa agggtagcag aaaacagctt cactcctcag gaagtacat ggacagacgc 1320
ctaccagggg tgacaaaagca gtgcagttgg attgtaagga aaaattccgg aattaatgca 1380

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tcctaata gaa tgttgtcccc ttcaatgggtg ttaccttagg agctgaacat tcaattcagt 1440
tacaccacta tgactaaaaa cagtttggat ctcttagtat tgcctttgaa actgcaacat 1500
aagcaactca acaatattag ttgcattcct ttatagacat accatgtcaa agacgttttt 1560
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gcaattggta tttgacttgg aagtgttgtg ttgtattttt tgaaccctta ggcttcagga 1920
aaactgctct tttgtaaaaa gaatagcgat gacattttct aatgtgcaga aatgttccaa 1980
aaggacaaaa ttgaaaacca aaaactatgt tattaaaaca aaaaaatgct aaaaaaaaaa 2040
aaaaaaaaa 2048

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<210> 189

<211> 336

<212> PRT

<213> Homo sapiens

<400> 189

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Met Lys Thr Leu Met Arg His Gly Leu Ala Val Cys Leu Ala Leu Thr
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Thr Met Cys Thr Ser Leu Leu Leu Val Tyr Ser Ser Leu Gly Gly Gln
          20           25           30
Lys Glu Arg Pro Pro Gln Gln Gln Gln Gln Gln Gln Gln Gln
          35           40           45
Gln Ala Ser Ala Thr Gly Ser Ser Gln Pro Ala Ala Glu Ser Ser Thr
          50           55           60
Gln Gln Arg Pro Gly Val Pro Ala Gly Pro Arg Pro Leu Asp Gly Tyr
65           70           75           80
Leu Gly Val Ala Asp His Lys Pro Leu Lys Met His Cys Arg Asp Cys
          85           90           95
Ala Leu Val Thr Ser Ser Gly His Leu Leu His Ser Arg Gln Gly Ser
          100          105          110
Gln Ile Asp Gln Thr Glu Cys Val Ile Arg Met Asn Asp Ala Pro Thr
          115          120          125
Arg Gly Tyr Gly Arg Asp Val Gly Asn Arg Thr Ser Leu Arg Val Ile
          130          135          140
Ala His Ser Ser Ile Gln Arg Ile Leu Arg Asn Arg His Asp Leu Leu
          145          150          155          160
Asn Val Ser Gln Gly Thr Val Phe Ile Phe Trp Gly Pro Ser Ser Tyr
          165          170          175
Met Arg Arg Asp Gly Lys Gly Gln Val Tyr Asn Asn Leu His Leu Leu
          180          185          190
Ser Gln Val Leu Pro Arg Leu Lys Ala Phe Met Ile Thr Arg His Lys
          195          200          205
Met Leu Gln Phe Asp Glu Leu Phe Lys Gln Glu Thr Gly Lys Asp Arg
          210          215          220
Lys Ile Ser Asn Thr Trp Leu Ser Thr Gly Trp Phe Thr Met Thr Ile
          225          230          235          240
Ala Leu Glu Leu Cys Asp Arg Ile Asn Val Tyr Gly Met Val Pro Pro
          245          250          255
Asp Phe Cys Arg Asp Pro Asn His Pro Ser Val Pro Tyr His Tyr Tyr
          260          265          270
Glu Pro Phe Gly Pro Asp Glu Cys Thr Met Tyr Leu Ser His Glu Arg
          275          280          285
Gly Arg Lys Gly Ser His His Arg Phe Ile Thr Glu Lys Arg Val Phe
          290          295          300
Lys Asn Trp Ala Arg Thr Phe Asn Ile His Phe Phe Gln Pro Asp Trp

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305 310 315 320
Lys Pro Glu Ser Leu Ala Ile Asn His Pro Glu Asn Lys Pro Val Phe
 325 330 335

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<210> 190
<211> 1078
<212> DNA
<213> Homo sapiens
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<400>	190						
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gccaacagtt	tagaagccaa	actcaaggag	atgcaaaaat	tctttggcct	acctataact	240	
ggaatgttaa	actccgcgt	catagaaata	atgcagaagc	ccagatgtgg	agtgccagat	300	
gttgcagaat	actcactatt	tccaaatagc	ccaaaatgga	cttccaaagt	ggtcacctac	360	
aggatcgtat	catatactcg	agacttaccg	catattacag	tggatcgatt	agtgtcaaag	420	
gctttaaaca	tgtggggcaa	agagatcccc	ctgcatttca	ggaaagttgt	atgggggaact	480	
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aaaggcattc	agaaaactata	tggaaagaga	agtaattcaa	gaaagaaata	gaaacttcag	840	
gcagaacatc	cattcattca	ttcattggat	tgtatatcat	tgttgcaaa	tcagaattga	900	
taagcactgt	tcctccactc	catttagcaa	ttatgtcacc	cttttttatt	gcagttgggt	960	
tttgaatgtc	tttcactcct	tttattgggt	aaactccttt	atggtgtgac	tgtgtcttat	1020	
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<210> 191
<211> 267
<212> PRT
<213> .Homo sapiens
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<400>	191															
Met	Arg	Leu	Thr	Val	Leu	Cys	Ala	Val	Cys	Leu	Leu	Pro	Gly	Ser	Leu	
1				5					10					15		
Ala	Leu	Pro	Leu	Pro	Gln	Glu	Ala	Gly	Gly	Met	Ser	Glu	Leu	Gln	Trp	
			20					25					30			
Glu	Gln	Ala	Gln	Asp	Tyr	Leu	Lys	Arg	Phe	Tyr	Leu	Tyr	Asp	Ser	Glu	
		35					40					45				
Thr	Lys	Asn	Ala	Asn	Ser	Leu	Glu	Ala	Lys	Leu	Lys	Glu	Met	Gln	Lys	
	50					55					60					
Phe	Phe	Gly	Leu	Pro	Ile	Thr	Gly	Met	Leu	Asn	Ser	Arg	Val	Ile	Glu	
65					70					75				80		
Ile	Met	Gln	Lys	Pro	Arg	Cys	Gly	Val	Pro	Asp	Val	Ala	Glu	Tyr	Ser	
				85					90					95		
Leu	Phe	Pro	Asn	Ser	Pro	Lys	Trp	Thr	Ser	Lys	Val	Val	Thr	Tyr	Arg	
			100					105					110			
Ile	Val	Ser	Tyr	Thr	Arg	Asp	Leu	Pro	His	Ile	Thr	Val	Asp	Arg	Leu	
		115					120					125				
Val	Ser	Lys	Ala	Leu	Asn	Met	Trp	Gly	Lys	Glu	Ile	Pro	Leu	His	Phe	
	130					135					140					
Arg	Lys	Val	Val	Trp	Gly	Thr	Ala	Asp	Ile	Met	Ile	Gly	Phe	Ala	Arg	
145					150				155						160	
Gly	Ala	His	Gly	Asp	Ser	Tyr	Pro	Phe	Asp	Gly	Pro	Gly	Asn	Thr	Leu	
				165					170					175		

196

Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe
 180 185 190
 Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe
 195 200 205
 Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His
 210 215 220
 Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp
 225 230 235 240
 Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys
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 Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys
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<210> 192

<211> 2217

<212> DNA

<213> Homo sapiens

<400> 192

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<210> 193
 <211> 702
 <212> PRT
 <213> Homo sapiens

<400> 193

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Ala	Leu	Gly	Ser	Leu	Leu	Phe	Leu	Leu	Phe	Ser	Leu	Gly	Trp	Val	Gln
			20					25					30		
Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu
		35					40					45			
Asp	Gly	Val	Leu	Ala	Asn	Pro	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg
	50				55						60				
Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu
65					70					75					80
Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu
				85					90					95	
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro
			100					105					110		
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro
	115						120					125			
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile
	130					135					140				
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln
145					150					155					160
Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu
				165					170					175	
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu
			180					185					190		
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu
		195					200					205			
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg
	210					215				220					
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp
225					230					235					240
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly
				245					250					255	
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg
		260						265					270		
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile
		275				280						285			
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser
	290					295					300				
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys
305					310					315					320
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met
				325					330					335	
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu
			340					345					350		
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val
		355					360					365			
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile
	370					375						380			
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu
385					390					395					400
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Ala	Pro	Arg	Arg	Pro	Leu
				405					410					415	

Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
 420 425 430
 Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
 435 440 445
 Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
 450 455 460
 Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
 465 470 475 480
 Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
 485 490 495
 Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
 500 505 510
 Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
 515 520 525
 Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
 530 535 540
 Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
 545 550 555 560
 Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
 565 570 575
 Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
 580 585 590
 Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Gly Arg Gly Gly Gln
 595 600 605
 Ala Arg Ala Gly Gly Arg Ala Gly Gly Val Glu Val Gly Ala Leu Ser
 610 615 620
 His Pro Ser Leu Cys Arg Gly Pro Leu Gly Asp Ala Leu Pro Pro Arg
 625 630 635 640
 Thr Trp Thr Cys Ser His Arg Pro Gly Thr Ala Pro Ser Leu His Pro
 645 650 655
 Gly Leu Arg Ala Pro Leu Pro Cys Trp Pro Gln Pro Cys Trp Gly Ser
 660 665 670
 Pro Pro Gly Gln Glu Gln Ala Arg Val Ile Pro Val Pro Pro Gln Glu
 675 680 685
 Asn Ser Arg Ser Val Asn Gly Asn Met Pro Pro Ala Asp Thr
 690 695 700

<210> 194
 <211> 2135
 <212> DNA
 <213> Homo sapiens

<400> 194
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 tcctgtggga ccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
 cagccctcga ggaccctggc tggagagaca gggcaggagg ctgcaccctt ggacggagtc 240
 ctggccaacc cacctaacat ttccagcctc tccctcgcgc aactccttgg cttcccgtgt 300
 gcgagggtgt ccggcctgag cacggagcgt gtccggggagc tggctgtggc cttggcacag 360
 aagaatgtca agctctcaac agagcagctg cgctgtctgg ctaccggct ctctgagccc 420
 cccgaggacc tggacgcct cccattggac ctgctgctat tctcaacc agatgcgttc 480
 tcggggcccc aggcctgcac ccgtttcttc tcccgcatca cgaaggccaa tgtggacctg 540
 ctcccgaggg gggctccga gcgacagcgg ctgctgcctg cggctctggc ctgctggggg 600
 gtgcgggggt ctctgctgag cgaggctgat gtgcgggctc tgggaggcct ggcttgcgac 660
 ctgcctgggc gctttgtggc cgagtcggcc gaagtgtctc taccgggt ggtgagctgc 720
 ccgggacccc tggaccagga ccagcaggag gcagccagg cggctctgca gggcggggga 780
 ccccccacg gcccccgctc gacatggtct gtctccacga tggacgctct gcggggcctg 840

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ctgcccgtgc tgggccagcc catcatccgc agcatcccgc agggcatcgt ggccgcgtgg 900
cggcaacgct cctctcggga cccatcctgg cggcagcctg aacggaccat cctccggccg 960
cggttccggc gggaagtggg gaagacagcc tgtccttcag gcaagaaggc ccgcgagata 1020
gacgagagcc tcatcttcta caagaagtgg gagctggaag cctgcgtgga tgcggccctg 1080
ctggccaccc agatggaccg cgtgaacgcc atccccttca cctacgagca gctggacgtc 1140
ctaaagcata aactggatga gctctacca caaggttacc ccgagtctgt gatccagcac 1200
ctgggctacc tcttctctca gatgagccct gaggacattc gcaagtggaa tgtgacgtcc 1260
ctggagaccc tgaaggcttt gcttgaagtc aacaaagggc acgaaatgag tcctcaggct 1320
cctcggcggc ccctcccaca ggtggccacc ctgatcgacc gctttgtgaa gggaaggggc 1380
cagctagaca aagacaccct agacaccctg accgccttct accctgggta cctgtgctcc 1440
ctcagccccc aggagctgag ctccgtgcc cccagcagca tctgggcggg caggcccccag 1500
gacctggaca cgtgtgaccc aaggcagctg gacgtcctct atcccaaggc ccgccttgc 1560
ttccagaaca tgaacgggtc cgaatacttc gtgaagatcc agtccttcct ggggtggggcc 1620
cccacggagg atttgaaggc gctcagtcag cagaatgtga gcatggactt ggccacgttc 1680
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ctacggcagc ggcaggacga cctggacacg ctggggctgg ggctacaggg cggcatcccc 1860
aacggctacc tggctctaga cctcagcgtg caagaggccc tctcggggac gccctgcctc 1920
ctaggacctg gacctgttct caccgtcctg gcaactgtcc tagcctccac cctggcctga 1980
gggccccact cccttgcctg cccagccct gctggggatc cccgcctggc caggagcagg 2040
cacgggtgat ccccgttcca cccaagaga actcgcgtc agtaaacggg aacatgcccc 2100
ctgcagacac gtaaaaaaaaa aaaaaaaaaa aaaaa 2135

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<210> 195

<211> 630

<212> PRT

<213> Homo sapiens

<400> 195

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Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
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Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
          20          25          30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
          35          40          45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
          50          55          60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
          65          70          75          80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
          85          90          95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
          100          105          110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
          115          120          125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
          130          135          140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
          145          150          155          160
Arg Leu Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
          165          170          175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
          180          185          190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
          195          200          205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
          210          215          220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp

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200

225					230					235				240
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu
				245					250					255
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp
			260					265					270	
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr
		275					280					285		
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro
	290					295					300			
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys
305					310					315				320
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln
				325				330						335
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val
			340				345						350	
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser
	355						360					365		
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp
	370					375					380			
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu
385					390					395				400
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Ala	Pro	Arg	Arg	Pro
			405						410					415
Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp	Arg	Phe	Val	Lys	Gly	Arg	Gly
		420						425					430	
Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	Leu	Thr	Ala	Phe	Tyr	Pro	Gly
	435					440					445			
Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	Leu	Ser	Ser	Val	Pro	Pro	Ser
	450					455				460				
Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	Leu	Asp	Thr	Cys	Asp	Pro	Arg
465					470					475				480
Leu	Asp	Val	Leu	Tyr	Pro	Lys	Ala	Arg	Leu	Ala	Phe	Gln	Asn	Met
			485					490					495	
Gly	Ser	Glu	Tyr	Phe	Val	Lys	Ile	Gln	Ser	Phe	Leu	Gly	Gly	Ala
		500						505					510	
Thr	Glu	Asp	Leu	Lys	Ala	Leu	Ser	Gln	Gln	Asn	Val	Ser	Met	Asp
	515						520					525		
Ala	Thr	Phe	Met	Lys	Leu	Arg	Thr	Asp	Ala	Val	Leu	Pro	Leu	Thr
	530					535					540			
Ala	Glu	Val	Gln	Lys	Leu	Leu	Gly	Pro	His	Val	Glu	Gly	Leu	Lys
545					550					555				560
Glu	Glu	Arg	His	Arg	Pro	Val	Arg	Asp	Trp	Ile	Leu	Arg	Gln	Arg
			565					570					575	
Asp	Asp	Leu	Asp	Thr	Leu	Gly	Leu	Gly	Leu	Gln	Gly	Gly	Ile	Pro
		580					585					590		
Gly	Tyr	Leu	Val	Leu	Asp	Leu	Ser	Val	Gln	Glu	Ala	Leu	Ser	Gly
	595					600						605		
Pro	Cys	Leu	Leu	Gly	Pro	Gly	Pro	Val	Leu	Thr	Val	Leu	Ala	Leu
	610					615					620			
Leu	Ala	Ser	Thr	Leu	Ala									
625					630									

<210> 196

<211> 2105

<212> DNA

<213> Homo sapiens

201

<400> 196

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cctccctccc tgggatctac acagaccatg gccttgccaa cggctcgacc cctgttgggg 120
tctgtgggga ccccgccct cggcagcctc ctgttcctgc tcttcagcct cggatgggtg 180
cagccctcga ggaccctggc tggagagaca gggcaggagg ctgcaccctt ggacggagtc 240
ctggccaacc cacctaacat ttccagcctc tcccctcgcc aactccttgg cttcccgtgt 300
gcggaggtgt ccggcctgag cacggagcgt gtccgggagc tggctgtggc cttggcacag 360
aagaatgtca agctctcaac agagcagctg cgctgtcttg ctacacggct ctctgagccc 420
ccggaggacc tggacgcctt cccattggac ctgctgctat tcccaacccc agatgcgttc 480
tcggggcccc aggcctgcac ccgtttcttc tcccgcata cgaaggccaa tgtggacctg 540
ctcccagggg gggctccga gcgacagcgg ctgctgcctg cggctctggc ctgctggggg 600
gtgcgggggt ctctgctgag cgaggctgat gtgcgggctc tgggaggcct ggcttgcgac 660
ctgctggggc gctttgtggc cgagtgggac gaagtgtgc taccctggct ggtgagctgc 720
ccgggacccc tggaccagga ccagcaggag gcagccaggg cggctctgca gggcggggga 780
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cggcaacgct cctctcgga cccatcctgg cggcagcctg aacggaccat cctccggccg 960
cggttccggc gggaagtgga gaagacagcc tgtccttcag gcaagaaggc ccgcgagata 1020
gacgagagcc tcatcttcta caagaagtgg gagctggaag cctgcgtgga tgcggccctg 1080
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gactggaca cgtgtgaccc aaggcagctg gacgtcctct atcccaaggc ccgccttgct 1560
ttccagaaca tgaacgggtc cgaatacttc gtgaagatcc agtccttctt ggggtggggc 1620
cccacggagg atttgaaggc gctcagtcag cagaatgtga gcatggactt ggccacgttc 1680
atgaagctgc ggacggatgc ggtgctgccc ttgactgtgg ctgaggtgca gaaacttctg 1740
ggacccacg tggaggcctt gaaggcggag gagcggcacc gcccggtgcg ggactggatc 1800
ctacggcagc ggcaggacga cctggacacg ctggggctgg ggctacaggg cggcatcccc 1860
aacggctacc tggctctaga cctcagcgtg caaggacctg gacctgttct caccgtcctg 1920
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gctggggatc cccgcctggc caggagcagg cacgggtgat ccccgttcca cccaagaga 2040
actcgcgtc agtaaaggc aacatgcccc ctgcagacac gtaaaaaaaa aaaaaaaaaa 2100
aaaaa 2105

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<210> 197

<211> 620

<212> PRT

<213> Homo sapiens

<400> 197

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Met Ala Leu Pro Thr Ala Arg Pro Leu Leu Gly Ser Cys Gly Thr Pro
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Ala Leu Gly Ser Leu Leu Phe Leu Leu Phe Ser Leu Gly Trp Val Gln
             20             25             30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
             35             40             45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
             50             55             60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
             65             70             75             80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
             85             90             95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
             100             105             110

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Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro	115	120	125
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile	130	135	140
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln	145	150	155
Arg	Leu	Leu	Pro	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu		165	170	175
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu	180	185	190
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu	195	200	205
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg	210	215	220
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp	225	230	235
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly	245	250	255
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg	260	265	270
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile	275	280	285
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser	290	295	300
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys	305	310	315
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met	325	330	335
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu	340	345	350
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val	355	360	365
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile	370	375	380
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu	385	390	395
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Ala	Pro	Arg	Arg	Pro	Leu	405	410	415
Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp	Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	420	425	430
Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	435	440	445
Leu	Cys	Ser	Leu	Ser	Pro	Glu	Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser		450	455	460
Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	Leu	Asp	Thr	Cys	Asp	Pro	Arg	Gln	465	470	475
Leu	Asp	Val	Leu	Tyr	Pro	Lys	Ala	Arg	Leu	Ala	Phe	Gln	Asn	Met	Asn	485	490	495
Gly	Ser	Glu	Tyr	Phe	Val	Lys	Ile	Gln	Ser	Phe	Leu	Gly	Gly	Ala	Pro	500	505	510
Thr	Glu	Asp	Leu	Lys	Ala	Leu	Ser	Gln	Gln	Asn	Val	Ser	Met	Asp	Leu	515	520	525
Ala	Thr	Phe	Met	Lys	Leu	Arg	Thr	Asp	Ala	Val	Leu	Pro	Leu	Thr	Val	530	535	540
Ala	Glu	Val	Gln	Lys	Leu	Leu	Gly	Pro	His	Val	Glu	Gly	Leu	Lys	Ala	545	550	555
Glu	Glu	Arg	His	Arg	Pro	Val	Arg	Asp	Trp	Ile	Leu	Arg	Gln	Arg	Gln	565	570	575

Asp	Asp	Leu	Asp	Thr	Leu	Gly	Leu	Gly	Leu	Gln	Gly	Gly	Ile	Pro	Asn
			580					585					590		
Gly	Tyr	Leu	Val	Leu	Asp	Leu	Ser	Val	Gln	Gly	Pro	Gly	Pro	Val	Leu
		595				600						605			
Thr	Val	Leu	Ala	Leu	Leu	Leu	Ala	Ser	Thr	Leu	Ala				
	610					615					620				

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<210> 198
<211> 2193
<212> DNA
<213> Homo sapiens
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<400> 198						
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tctgtggga	ccccgcct	cggcagcctc	ctgttctctgc	tcttcagcct	cggatgggtg	180
cagccctcga	ggaccctggc	tggagagaca	gggcaggagg	ctgcacccct	ggacggagtc	240
ctggccaacc	cacctaacat	ttccagcctc	tccctcgcc	aactccttgg	cttcccggtg	300
gcggaggtgt	ccggcctgag	cacggagcgt	gtccgggagc	tggctgtggc	cttggcacag	360
aagaatgtca	agctctcaac	agagcagctg	cgctgtctgg	ctcacgggct	ctctgagccc	420
cccgaggacc	tggacgcct	cccattggac	ctgctgctat	tcctcaaccc	agatgcgttc	480
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<210> 199
<211> 694
<212> PRT
<213> Homo sapiens
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<400> 199

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Ala	Leu	Gly	Ser	Leu	Leu	Phe	Leu	Leu	Phe	Ser	Leu	Gly	Trp	Val	Gln	20	25	30	
Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu	35	40	45	
Asp	Gly	Val	Leu	Ala	Asn	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg		50	55	60	
Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu	65	70	75	80
Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu	85	90	95	
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro	100	105	110	
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro	115	120	125	
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile	130	135	140	
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln	145	150	155	160
Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu	165	170	175	
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu	180	185	190	
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu	195	200	205	
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg	210	215	220	
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp	225	230	235	240
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly	245	250	255	
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg	260	265	270	
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile	275	280	285	
Leu	Arg	Pro	Arg	Phe	Arg	Arg	Glu	Val	Glu	Lys	Thr	Ala	Cys	Pro	Ser	290	295	300	
Gly	Lys	Lys	Ala	Arg	Glu	Ile	Asp	Glu	Ser	Leu	Ile	Phe	Tyr	Lys	Lys	305	310	315	320
Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met	325	330	335	
Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu	340	345	350	
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val	355	360	365	
Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile	370	375	380	
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu	385	390	395	400
Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp	405	410	415	
Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr	420	425	430	
Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu	435	440	445	
Leu	Ser	Ser	Val	Pro	Pro	Ser	Ser	Ile	Trp	Ala	Val	Arg	Pro	Gln	Asp	450	455	460	

Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala
 465 470 475 480
 Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
 485 490 495
 Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
 500 505 510
 Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
 515 520 525
 Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
 530 535 540
 Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
 545 550 555 560
 Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
 565 570 575
 Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
 580 585 590
 Val Gln Gly Gly Arg Gly Gly Gln Ala Arg Ala Gly Gly Arg Ala Gly
 595 600 605
 Gly Val Glu Val Gly Ala Leu Ser His Pro Ser Leu Cys Arg Gly Pro
 610 615 620
 Leu Gly Asp Ala Leu Pro Pro Arg Thr Trp Thr Cys Ser His Arg Pro
 625 630 635 640
 Gly Thr Ala Pro Ser Leu His Pro Gly Leu Arg Ala Pro Leu Pro Cys
 645 650 655
 Trp Pro Gln Pro Cys Trp Gly Ser Pro Pro Gly Gln Glu Gln Ala Arg
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 675 680 685
 Met Pro Pro Ala Asp Thr
 690

<210> 200
 <211> 2081
 <212> DNA
 <213> Homo sapiens

<400> 200
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 ctggccaacc cacctaaccat ttccagcctc tcccctcgcc aactccttgg cttcccgtgt 300
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 aagaatgtca agctctcaac agagcagctg cgctgtcttg ctcaccggct ctctgagccc 420
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<210> 201
 <211> 612
 <212> PRT
 <213> Homo sapiens

<400> 201

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Ala	Leu	Gly	Ser	Leu	Leu	Phe	Leu	Leu	Phe	Ser	Leu	Gly	Trp	Val	Gln
			20					25					30		
Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu
		35					40					45			
Asp	Gly	Val	Leu	Ala	Asn	Pro	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg
	50				55					60					
Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu
65					70					75					80
Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu
			85					90						95	
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro
		100						105					110		
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro
	115						120					125			
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile
	130					135					140				
Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln
145				150						155					160
Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu
			165					170						175	
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu
		180						185					190		
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu
	195						200						205		
Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg
	210					215					220				
Ala	Ala	Leu	Gln	Gly	Gly	Gly	Pro	Pro	Tyr	Gly	Pro	Pro	Ser	Thr	Trp
225					230					235					240
Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly
			245						250					255	
Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg
		260						265					270		
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile
	275						280						285		

Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
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 Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
 305 310 315 320
 Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
 325 330 335
 Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
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 Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
 355 360 365
 Ile Gln His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile
 370 375 380
 Arg Lys Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu
 385 390 395 400
 Val Asn Lys Gly His Glu Met Ser Pro Gln Val Ala Thr Leu Ile Asp
 405 410 415
 Arg Phe Val Lys Gly Arg Gly Gln Leu Asp Lys Asp Thr Leu Asp Thr
 420 425 430
 Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys Ser Leu Ser Pro Glu Glu
 435 440 445
 Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp
 450 455 460
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 465 470 475 480
 Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile
 485 490 495
 Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser
 500 505 510
 Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr
 515 520 525
 Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly
 530 535 540
 Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg
 545 550 555 560
 Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu
 565 570 575
 Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser
 580 585 590
 Val Gln Gly Pro Gly Pro Val Leu Thr Val Leu Ala Leu Leu Leu Ala
 595 600 605
 Ser Thr Leu Ala
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<210> 202

<211> 1195

<212> DNA

<213> Homo sapiens

<400> 202

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 gaccgcgtga acgccatccc cttcacctac gagcagctgg acgtcctaaa gcataaactg 180
 gatgagctct acccacaagg ttaccccgag tctgtgatcc agcacctggg ctacctcttc 240
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 gctttgcttg aagtcaacaa agggcacgaa atgagtcctc aggtggccac cctgatcgac 360
 cgctttgtga aggggaagggg ccagctagac aaagacaccc tagacaccct gaccgccttc 420
 taccctgggt acctgtgctc cctcagcccc gaggagctga gctccgtgcc cccagcagc 480

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cagtccttcc tgggtggggc cccacaggag gatttgaagg cgctcagtca gcagaatgtg 660
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<210> 203

<211> 398

<212> PRT

<213> Homo sapiens

<400> 203

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20     25     30
Ala Ala Leu Leu Ala Thr Gln Met Asp Arg Val Asn Ala Ile Pro Phe
35     40     45
Thr Tyr Glu Gln Leu Asp Val Leu Lys His Lys Leu Asp Glu Leu Tyr
50     55     60
Pro Gln Gly Tyr Pro Glu Ser Val Ile Gln His Leu Gly Tyr Leu Phe
65     70     75     80
Leu Lys Met Ser Pro Glu Asp Ile Arg Lys Trp Asn Val Thr Ser Leu
85     90     95
Glu Thr Leu Lys Ala Leu Leu Glu Val Asn Lys Gly His Glu Met Ser
100    105    110
Pro Gln Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln
115    120    125
Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
130    135    140
Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
145    150    155    160
Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
165    170    175
Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
180    185    190
Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
195    200    205
Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
210    215    220
Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
225    230    235    240
Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
245    250    255
Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
260    265    270
Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
275    280    285
Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Gly Gly Arg Gly Gly Gln
290    295    300
Ala Arg Ala Gly Gly Arg Ala Gly Gly Val Glu Val Gly Ala Leu Ser

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209

305		310		315		320									
His	Pro	Ser	Leu	Cys	Arg	Gly	Pro	Leu	Gly	Asp	Ala	Leu	Pro	Pro	Arg
				325					330					335	
Thr	Trp	Thr	Cys	Ser	His	Arg	Pro	Gly	Thr	Ala	Pro	Ser	Leu	His	Pro
			340					345					350		
Gly	Leu	Arg	Ala	Pro	Leu	Pro	Cys	Trp	Pro	Gln	Pro	Cys	Trp	Gly	Ser
		355					360					365			
Pro	Pro	Gly	Gln	Glu	Gln	Ala	Arg	Val	Ile	Pro	Val	Pro	Pro	Gln	Glu
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Asn	Ser	Arg	Ser	Val	Asn	Gly	Asn	Met	Pro	Pro	Ala	Asp	Thr		
385				390						395					

<210> 204
 <211> 2085
 <212> DNA
 <213> Homo sapiens

<400> 204

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<210> 205
 <211> 622
 <212> PRT

<213> Homo sapiens

<400> 205

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		20						25					30		
Pro	Ser	Arg	Thr	Leu	Ala	Gly	Glu	Thr	Gly	Gln	Glu	Ala	Ala	Pro	Leu
		35					40					45			
Asp	Gly	Val	Leu	Ala	Asn	Pro	Pro	Asn	Ile	Ser	Ser	Leu	Ser	Pro	Arg
	50				55						60				
Gln	Leu	Leu	Gly	Phe	Pro	Cys	Ala	Glu	Val	Ser	Gly	Leu	Ser	Thr	Glu
65				70						75					80
Arg	Val	Arg	Glu	Leu	Ala	Val	Ala	Leu	Ala	Gln	Lys	Asn	Val	Lys	Leu
				85					90					95	
Ser	Thr	Glu	Gln	Leu	Arg	Cys	Leu	Ala	His	Arg	Leu	Ser	Glu	Pro	Pro
		100						105					110		
Glu	Asp	Leu	Asp	Ala	Leu	Pro	Leu	Asp	Leu	Leu	Leu	Phe	Leu	Asn	Pro
	115						120					125			
Asp	Ala	Phe	Ser	Gly	Pro	Gln	Ala	Cys	Thr	Arg	Phe	Phe	Ser	Arg	Ile
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Thr	Lys	Ala	Asn	Val	Asp	Leu	Leu	Pro	Arg	Gly	Ala	Pro	Glu	Arg	Gln
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Arg	Leu	Leu	Pro	Ala	Ala	Leu	Ala	Cys	Trp	Gly	Val	Arg	Gly	Ser	Leu
				165					170					175	
Leu	Ser	Glu	Ala	Asp	Val	Arg	Ala	Leu	Gly	Gly	Leu	Ala	Cys	Asp	Leu
		180						185					190		
Pro	Gly	Arg	Phe	Val	Ala	Glu	Ser	Ala	Glu	Val	Leu	Leu	Pro	Arg	Leu
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Val	Ser	Cys	Pro	Gly	Pro	Leu	Asp	Gln	Asp	Gln	Gln	Glu	Ala	Ala	Arg
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Ser	Val	Ser	Thr	Met	Asp	Ala	Leu	Arg	Gly	Leu	Leu	Pro	Val	Leu	Gly
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Gln	Pro	Ile	Ile	Arg	Ser	Ile	Pro	Gln	Gly	Ile	Val	Ala	Ala	Trp	Arg
		260						265					270		
Gln	Arg	Ser	Ser	Arg	Asp	Pro	Ser	Trp	Arg	Gln	Pro	Glu	Arg	Thr	Ile
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Trp	Glu	Leu	Glu	Ala	Cys	Val	Asp	Ala	Ala	Leu	Leu	Ala	Thr	Gln	Met
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Asp	Arg	Val	Asn	Ala	Ile	Pro	Phe	Thr	Tyr	Glu	Gln	Leu	Asp	Val	Leu
		340						345					350		
Lys	His	Lys	Leu	Asp	Glu	Leu	Tyr	Pro	Gln	Gly	Tyr	Pro	Glu	Ser	Val
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Ile	Gln	His	Leu	Gly	Tyr	Leu	Phe	Leu	Lys	Met	Ser	Pro	Glu	Asp	Ile
	370					375						380			
Arg	Lys	Trp	Asn	Val	Thr	Ser	Leu	Glu	Thr	Leu	Lys	Ala	Leu	Leu	Glu
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Val	Asn	Lys	Gly	His	Glu	Met	Ser	Pro	Gln	Val	Ala	Thr	Leu	Ile	Asp
				405					410					415	
Arg	Phe	Val	Lys	Gly	Arg	Gly	Gln	Leu	Asp	Lys	Asp	Thr	Leu	Asp	Thr
		420						425					430		
Leu	Thr	Ala	Phe	Tyr	Pro	Gly	Tyr	Leu	Cys	Ser	Leu	Ser	Pro	Glu	Glu

435	440	445
Leu Ser Ser Val Pro Pro Ser Ser Ile Trp Ala Val Arg Pro Gln Asp		
450	455	460
Leu Asp Thr Cys Asp Pro Arg Gln Leu Asp Val Leu Tyr Pro Lys Ala		
465	470	475
Arg Leu Ala Phe Gln Asn Met Asn Gly Ser Glu Tyr Phe Val Lys Ile		
485	490	495
Gln Ser Phe Leu Gly Gly Ala Pro Thr Glu Asp Leu Lys Ala Leu Ser		
500	505	510
Gln Gln Asn Val Ser Met Asp Leu Ala Thr Phe Met Lys Leu Arg Thr		
515	520	525
Asp Ala Val Leu Pro Leu Thr Val Ala Glu Val Gln Lys Leu Leu Gly		
530	535	540
Pro His Val Glu Gly Leu Lys Ala Glu Glu Arg His Arg Pro Val Arg		
545	550	555
Asp Trp Ile Leu Arg Gln Arg Gln Asp Asp Leu Asp Thr Leu Gly Leu		
565	570	575
Gly Leu Gln Gly Gly Ile Pro Asn Gly Tyr Leu Val Leu Asp Leu Ser		
580	585	590
Val Gln Glu Ala Leu Ser Gly Thr Pro Cys Leu Leu Gly Pro Gly Pro		
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Val Leu Thr Val Leu Ala Leu Leu Leu Ala Ser Thr Leu Ala		
610	615	620

<210> 206

<211> 2111

<212> DNA

<213> Homo sapiens

<400> 206

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aaaaaaaaaa a                                     2111

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<210> 207

<211> 2107

<212> DNA

<213> Homo sapiens

<400> 207

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<210> 208

<211> 628

<212> PRT

<213> Homo sapiens

<400> 208

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 20      25      30
Arg Thr Leu Ala Gly Glu Thr Gly Thr Glu Ser Ala Pro Leu Gly Gly
 35      40      45
Val Leu Thr Thr Pro His Asn Ile Ser Ser Leu Ser Pro Arg Gln Leu
 50      55      60
Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu Arg Val
 65      70      75      80
Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu Ser Thr
 85      90      95
Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro Glu Asp
100      105      110
Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro Asp Ala
115      120      125
Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile Thr Lys
130      135      140
Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln Arg Leu
145      150      155      160
Leu Pro Ala Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu Leu Ser
165      170      175
Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu Pro Gly
180      185      190
Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu Val Ser
195      200      205
Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg Ala Ala
210      215      220
Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp Ser Val
225      230      235      240
Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly Gln Pro
245      250      255
Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg Gln Arg
260      265      270
Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile Leu Arg
275      280      285
Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser Gly Lys
290      295      300
Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys Trp Glu
305      310      315      320
Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met Asp Arg
325      330      335
Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu Lys His
340      345      350
Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val Ile Gln
355      360      365
His Leu Gly Tyr Leu Phe Leu Lys Met Ser Pro Glu Asp Ile Arg Lys
370      375      380
Trp Asn Val Thr Ser Leu Glu Thr Leu Lys Ala Leu Leu Glu Val Asp
385      390      395      400
Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu Pro Gln
405      410      415
Val Ala Thr Leu Ile Asp Arg Phe Val Lys Gly Arg Gly Gln Leu Asp
420      425      430
Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr Leu Cys
435      440      445
Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser Ile Trp

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450	455	460
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465	470	475
Val Leu Tyr Pro Lys Ala	Arg Leu Ala Phe Gln	Asn Met Asn Gly Ser
485	490	495
Glu Tyr Phe Val Lys Ile	Gln Ser Phe Leu Gly	Gly Ala Pro Thr Glu
500	505	510
Asp Leu Lys Ala Leu Ser	Gln Gln Asn Val Ser	Met Asp Leu Ala Thr
515	520	525
Phe Met Lys Leu Arg Thr	Asp Ala Val Leu Pro	Leu Thr Val Ala Glu
530	535	540
Val Gln Lys Leu Leu Gly	Pro His Val Glu Gly	Leu Lys Ala Glu Glu
545	550	555
Arg His Arg Pro Val Arg	Asp Trp Ile Leu Arg	Gln Arg Gln Asp Asp
565	570	575
Leu Asp Thr Leu Gly Leu	Gly Leu Gln Gly Gly	Ile Pro Asn Gly Tyr
580	585	590
Leu Val Leu Asp Leu Ser	Val Gln Glu Thr Leu	Ser Gly Thr Pro Cys
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610	615	620
Ser Thr Leu Ala		
625		

<210> 209

<211> 2316

<212> DNA

<213> Homo sapiens

<400> 209

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<210> 210

<211> 630

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(630)

<223> Xaa = Any Amino Acid

<400> 210

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20     25     30
Pro Ser Arg Thr Leu Ala Gly Glu Thr Gly Gln Glu Ala Ala Pro Leu
35     40     45
Asp Gly Val Leu Ala Asn Pro Pro Asn Ile Ser Ser Leu Ser Pro Arg
50     55     60
Gln Leu Leu Gly Phe Pro Cys Ala Glu Val Ser Gly Leu Ser Thr Glu
65     70     75     80
Arg Val Arg Glu Leu Ala Val Ala Leu Ala Gln Lys Asn Val Lys Leu
85     90     95
Ser Thr Glu Gln Leu Arg Cys Leu Ala His Arg Leu Ser Glu Pro Pro
100    105    110
Glu Asp Leu Asp Ala Leu Pro Leu Asp Leu Leu Leu Phe Leu Asn Pro
115    120    125
Asp Ala Phe Ser Gly Pro Gln Ala Cys Thr Arg Phe Phe Ser Arg Ile
130    135    140
Thr Lys Ala Asn Val Asp Leu Leu Pro Arg Gly Ala Pro Glu Arg Gln
145    150    155    160
Arg Leu Leu Pro Ala Leu Ala Cys Trp Gly Val Arg Gly Ser Leu
165    170    175
Leu Ser Glu Ala Asp Val Arg Ala Leu Gly Gly Leu Ala Cys Asp Leu
180    185    190
Pro Gly Arg Phe Val Ala Glu Ser Ala Glu Val Leu Leu Pro Arg Leu
195    200    205
Val Ser Cys Pro Gly Pro Leu Asp Gln Asp Gln Gln Glu Ala Ala Arg
210    215    220
Ala Ala Leu Gln Gly Gly Gly Pro Pro Tyr Gly Pro Pro Ser Thr Trp
225    230    235    240
Ser Val Ser Thr Met Asp Ala Leu Arg Gly Leu Leu Pro Val Leu Gly
245    250    255
Gln Pro Ile Ile Arg Ser Ile Pro Gln Gly Ile Val Ala Ala Trp Arg
260    265    270

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216

Gln Arg Ser Ser Arg Asp Pro Ser Trp Arg Gln Pro Glu Arg Thr Ile
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 Leu Arg Pro Arg Phe Arg Arg Glu Val Glu Lys Thr Ala Cys Pro Ser
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 Gly Lys Lys Ala Arg Glu Ile Asp Glu Ser Leu Ile Phe Tyr Lys Lys
 305 310 315 320
 Trp Glu Leu Glu Ala Cys Val Asp Ala Ala Leu Leu Ala Thr Gln Met
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 Asp Arg Val Asn Ala Ile Pro Phe Thr Tyr Glu Gln Leu Asp Val Leu
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 Lys His Lys Leu Asp Glu Leu Tyr Pro Gln Gly Tyr Pro Glu Ser Val
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 Val Asp Lys Gly His Glu Met Ser Pro Gln Ala Pro Arg Arg Pro Leu
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 420 425 430
 Leu Asp Lys Asp Thr Leu Asp Thr Leu Thr Ala Phe Tyr Pro Gly Tyr
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 Leu Cys Ser Leu Ser Pro Glu Glu Leu Ser Ser Val Pro Pro Ser Ser
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 Ile Trp Ala Val Arg Pro Gln Asp Leu Asp Thr Cys Asp Pro Arg Gln
 465 470 475 480
 Leu Asp Val Leu Tyr Pro Lys Ala Arg Leu Ala Phe Gln Asn Met Asn
 485 490 495
 Gly Ser Glu Tyr Phe Val Lys Ile Gln Ser Phe Leu Gly Gly Ala Pro
 500 505 510
 Thr Glu Asp Leu Lys Ala Leu Ser Gln Gln Asn Val Ser Met Asp Leu
 515 520 525
 Ala Thr Phe Met Lys Leu Arg Thr Asp Ala Val Leu Pro Leu Thr Val
 530 535 540
 Ala Glu Val Gln Lys Leu Leu Gly Pro His Val Glu Gly Leu Lys Ala
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 Glu Glu Arg His Arg Pro Val Arg Asp Trp Ile Leu Arg Gln Arg Gln
 565 570 575
 Asp Asp Leu Asp Thr Leu Gly Leu Gly Leu Gln Gly Gly Ile Pro Asn
 580 585 590
 Gly Tyr Leu Val Leu Asp Leu Ser Val Gln Xaa Xaa Leu Ser Gly Thr
 595 600 605
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 610 615 620
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 625 630

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 <211> 1721
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 <213> Homo sapiens

<400> 211
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<210> 212

<211> 515

<212> PRT

<213> Homo sapiens

<400> 212

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Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser
  35           40           45
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His
  50           55           60
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu
  65           70           75           80
Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln
  85           90           95
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr
  100          105          110
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro
  115          120          125
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr
  130          135          140
Arg Pro Pro Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser
  145          150          155          160
Ala Pro Asp Thr Arg Pro Pro Pro Gly Ser Thr Ala Pro Ala Ala His
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Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala
  180          185          190
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn Arg Pro Ala Leu
  195          200          205

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218

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Ala	Ser	Gly	Ser	Ala	Ser	Thr	Leu	Val	His	Asn	Gly	Thr	Ser	Ala	Arg
225					230					235					240
Ala	Thr	Thr	Thr	Pro	Ala	Ser	Lys	Ser	Thr	Pro	Phe	Ser	Ile	Pro	Ser
				245						250					255
His	His	Ser	Asp	Thr	Pro	Thr	Thr	Leu	Ala	Ser	His	Ser	Thr	Lys	Thr
			260						265						270
Asp	Ala	Ser	Ser	Thr	His	His	Ser	Thr	Val	Pro	Pro	Leu	Thr	Ser	Ser
			275						280						285
Asn	His	Ser	Thr	Ser	Pro	Gln	Leu	Ser	Thr	Gly	Val	Ser	Phe	Phe	Phe
			290						295						300
Leu	Ser	Phe	His	Ile	Ser	Asn	Leu	Gln	Phe	Asn	Ser	Ser	Leu	Glu	Asp
305					310					315					320
Pro	Ser	Thr	Asp	Tyr	Tyr	Gln	Glu	Leu	Gln	Arg	Asp	Ile	Ser	Glu	Met
				325						330					335
Phe	Leu	Gln	Ile	Tyr	Lys	Gln	Gly	Gly	Phe	Leu	Gly	Leu	Ser	Asn	Ile
			340						345						350
Lys	Phe	Arg	Pro	Gly	Ser	Val	Val	Val	Gln	Leu	Thr	Leu	Ala	Phe	Arg
			355						360						365
Glu	Gly	Thr	Ile	Asn	Val	His	Asp	Val	Glu	Thr	Gln	Phe	Asn	Gln	Tyr
			370				375								380
Lys	Thr	Glu	Ala	Ala	Ser	Arg	Tyr	Asn	Leu	Thr	Ile	Ser	Asp	Val	Ser
385					390					395					400
Val	Ser	Asp	Val	Pro	Phe	Pro	Phe	Ser	Ala	Gln	Ser	Gly	Ala	Gly	Val
				405						410					415
Pro	Gly	Trp	Gly	Ile	Ala	Leu	Leu	Val	Leu	Val	Cys	Val	Leu	Val	Ala
			420						425						430
Leu	Ala	Ile	Val	Tyr	Leu	Ile	Ala	Leu	Ala	Val	Cys	Gln	Cys	Arg	Arg
			435						440						445
Lys	Asn	Tyr	Gly	Gln	Leu	Asp	Ile	Phe	Pro	Ala	Arg	Asp	Thr	Tyr	His
			450				455								460
Pro	Met	Ser	Glu	Tyr	Pro	Thr	Tyr	His	Thr	His	Gly	Arg	Tyr	Val	Pro
465					470					475					480
Pro	Ser	Ser	Thr	Asp	Arg	Ser	Pro	Tyr	Glu	Lys	Val	Ser	Ala	Gly	Asn
				485						490					495
Gly	Gly	Ser	Ser	Leu	Ser	Tyr	Thr	Asn	Pro	Ala	Val	Ala	Ala	Thr	Ser
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Ala	Asn	Leu													
			515												

<210> 213

<211> 5793

<212> DNA

<213> Homo sapiens

<400> 213

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<211> 1783

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

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<223> Xaa = Any Amino Acid

<400> 214

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Tyr Val Asn Gly Phe Asn Pro Trp Ser Ser Val Pro Thr Thr Ser Thr
 35           40           45
Pro Gly Thr Ser Thr Val His Leu Ala Thr Ser Gly Thr Pro Ser Ser
 50           55           60
Leu Pro Gly His Thr Ala Pro Val Pro Leu Leu Ile Pro Phe Thr Leu
 65           70           75           80
Asn Phe Thr Ile Thr Asn Leu His Tyr Glu Glu Asn Met Gln His Pro
 85           90           95
Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu
100          105          110
Lys Pro Leu Phe Lys Ser Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys
115          120          125
Arg Leu Thr Leu Leu Arg Pro Glu Lys His Gly Ala Ala Thr Gly Val

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165	170	175
Glu Leu Gly Pro Tyr	Thr Leu Asp Arg Asp	Ser Leu Tyr Val Asn Gly
180	185	190
Phe Thr His Arg Ser	Ser Val Pro Thr Thr	Ser Ile Pro Gly Thr Ser
195	200	205
Ala Val His Leu Glu	Thr Ser Gly Thr Pro	Ala Ser Leu Pro Gly His
210	215	220
Thr Ala Pro Gly Pro	Leu Leu Val Pro Phe	Thr Leu Asn Phe Thr Ile
225	230	235
Thr Asn Leu Gln Tyr	Glu Glu Asp Met Arg	His Pro Gly Ser Arg Lys
245	250	255
Phe Asn Thr Thr Glu	Arg Val Leu Gln Gly	Leu Leu Lys Pro Leu Phe
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Lys Ser Thr Ser Val	Gly Pro Leu Tyr Ser	Gly Cys Arg Leu Thr Leu
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Leu Arg Pro Glu Lys	Arg Gly Ala Ala Thr	Gly Val Asp Thr Ile Cys
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Thr His Arg Leu Asp	Pro Leu Asn Pro Gly	Leu Asp Arg Glu Gln Leu
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325	330	335
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405	410	415
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Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser
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Asn	Cys	Asp	Gly	His	Ser	Met	Thr	Leu	Gly	Trp	Lys	Val	Pro	Lys	Phe
				725					730					735	
Ser	Gly	Gly	Ser	Pro	Ile	Leu	Gly	Tyr	Tyr	Leu	Asp	Lys	Arg	Glu	Val
			740					745					750		
His	His	Lys	Asn	Trp	His	Glu	Val	Asn	Ser	Ser	Pro	Ser	Lys	Pro	Thr
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Ile	Leu	Thr	Val	Asp	Gly	Leu	Thr	Glu	Gly	Ser	Leu	Tyr	Glu	Phe	Lys
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Ile	Ala	Ala	Val	Asn	Leu	Ala	Gly	Ile	Gly	Glu	Pro	Ser	Asp	Pro	Ser
785					790					795					800
Glu	His	Phe	Lys	Cys	Glu	Ala	Trp	Thr	Met	Pro	Glu	Pro	Gly	Pro	Ala
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Tyr	Asp	Leu	Thr	Phe	Cys	Glu	Val	Arg	Asp	Thr	Ser	Leu	Val	Met	Leu
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Trp	Lys	Ala	Pro	Val	Tyr	Ser	Gly	Ser	Ser	Pro	Val	Ser	Gly	Tyr	Phe
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1425	1430	1435	1440
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<210> 220
 <211> 4135
 <212> DNA
 <213> Homo sapiens

<400> 220

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<210> 221

<211> 689

<212> PRT

<213> Homo sapiens

<400> 221

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          20          25          30
Lys Glu Thr Asn Lys Asn Asn Thr Glu Ala Pro Val Thr Lys Ile Glu
          35          40          45
Leu Leu Pro Ser Tyr Ser Thr Ala Thr Leu Ile Asp Glu Pro Thr Glu
          50          55          60
Val Asp Asp Pro Trp Asn Leu Pro Thr Leu Gln Asp Ser Gly Ile Lys
65          70          75          80
Trp Ser Glu Arg Asp Thr Lys Gly Lys Ile Leu Cys Phe Phe Gln Gly
          85          90          95
Ile Gly Arg Leu Ile Leu Leu Leu Gly Phe Leu Tyr Phe Phe Val Cys
          100          105          110
Ser Leu Asp Ile Leu Ser Ser Ala Phe Gln Leu Val Gly Gly Lys Met
          115          120          125
Ala Gly Gln Phe Phe Ser Asn Ser Ser Ile Met Ser Asn Pro Leu Leu
          130          135          140
Gly Leu Val Ile Gly Val Leu Val Thr Val Leu Val Gln Ser Ser Ser
145          150          155          160
Thr Ser Thr Ser Ile Val Val Ser Met Val Ser Ser Ser Leu Leu Thr
          165          170          175
Val Arg Ala Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly Thr Ser
          180          185          190
Ile Thr Asn Thr Ile Val Ala Leu Met Gln Val Gly Asp Arg Ser Glu
          195          200          205
Phe Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe Asn Trp

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240

210	215	220
Leu Ser Leu Leu Val	Leu Leu Pro Val Glu	Val Ala Thr His Tyr Leu
225	230	235
Glu Ile Ile Thr Gln	Leu Ile Val Glu Ser Phe	His Phe Lys Asn Gly
245	250	255
Glu Asp Ala Pro Asp	Leu Leu Lys Val Ile Thr	Lys Pro Phe Thr Lys
260	265	270
Leu Ile Val Gln Leu	Asp Lys Lys Val Ile Ser	Gln Ile Ala Met Asn
275	280	285
Asp Glu Lys Ala Lys	Asn Lys Ser Leu Val Lys	Ile Trp Cys Lys Thr
290	295	300
Phe Thr Asn Lys Thr	Gln Ile Asn Val Thr Val	Pro Ser Thr Ala Asn
305	310	315
Cys Thr Ser Pro Ser	Leu Cys Trp Thr Asp Gly	Ile Gln Asn Trp Thr
325	330	335
Met Lys Asn Val Thr	Tyr Lys Glu Asn Ile Ala	Lys Cys Gln His Ile
340	345	350
Phe Val Asn Phe His	Ileu Pro Asp Leu Ala Val	Gly Thr Ile Leu Leu
355	360	365
Ile Leu Ser Leu Leu	Val Leu Cys Gly Cys Leu	Ile Met Ile Val Lys
370	375	380
Ile Leu Gly Ser Val	Leu Lys Gly Gln Val Ala	Thr Val Ile Lys Lys
385	390	395
Thr Ile Asn Thr Asp	Phe Pro Phe Pro Phe Ala	Trp Leu Thr Gly Tyr
405	410	415
Leu Ala Ile Leu Val	Gly Ala Gly Met Thr Phe	Ile Val Gln Ser Ser
420	425	430
Ser Val Phe Thr Ser	Ala Leu Thr Pro Leu Ile	Gly Ile Gly Val Ile
435	440	445
Thr Ile Glu Arg Ala	Tyr Pro Leu Thr Leu Gly	Ser Asn Ile Gly Thr
450	455	460
Thr Thr Thr Ala Ile	Leu Ala Ala Leu Ala Ser	Pro Gly Asn Ala Leu
465	470	475
Arg Ser Ser Leu Gln	Ile Ala Leu Cys His Phe	Phe Phe Asn Ile Ser
485	490	495
Gly Ile Leu Leu Trp	Tyr Pro Ile Pro Phe Thr	Arg Leu Pro Ile Arg
500	505	510
Met Ala Lys Gly Leu	Gly Asn Ile Ser Ala Lys	Tyr Arg Trp Phe Ala
515	520	525
Val Phe Tyr Leu Ile	Ile Phe Phe Phe Leu Ile	Pro Leu Thr Val Phe
530	535	540
Gly Leu Ser Leu Ala	Gly Trp Arg Val Leu Val	Gly Val Gly Val Pro
545	550	555
Val Val Phe Ile Ile	Ile Leu Val Leu Cys Leu	Arg Leu Leu Gln Ser
565	570	575
Arg Cys Pro Arg Val	Leu Pro Lys Lys Leu Gln	Asn Trp Asn Phe Leu
580	585	590
Pro Leu Trp Met Arg	Ser Leu Lys Pro Trp Asp	Ala Val Ser Lys
595	600	605
Phe Thr Gly Cys Phe	Gln Met Arg Cys Cys Cys	Cys Cys Arg Val Cys
610	615	620
Cys Arg Ala Cys Cys	Leu Leu Cys Gly Cys Pro	Lys Cys Cys Arg Cys
625	630	635
Ser Lys Cys Cys Glu	Asp Leu Glu Glu Ala Gln	Glu Gly Gln Asp Val
645	650	655
Pro Val Lys Ala Pro	Glu Thr Phe Asp Asn Ile	Thr Ile Ser Arg Glu
660	665	670
Ala Gln Gly Glu Val	Pro Ala Ser Asp Ser Lys	Thr Glu Cys Thr Ala

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Leu

<210> 222
 <211> 771
 <212> DNA
 <213> Homo sapiens

<400> 222

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<210> 223
 <211> 212
 <212> PRT
 <213> Homo sapiens

<400> 223

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      20           25           30
Ile Ile Leu Arg Ser Gly Phe Thr Ile Val Gln Arg Arg Lys Leu Arg
      35           40           45
Leu Ser Pro Glu Gln Cys Ser Asn Phe Tyr Val Glu Lys Tyr Gly Lys
      50           55           60
Met Phe Phe Pro Asn Leu Thr Ala Tyr Met Ser Ser Gly Pro Leu Val
      65           70           75           80
Ala Met Ile Leu Ala Arg His Lys Ala Ile Ser Tyr Trp Leu Glu Leu
      85           90           95
Leu Gly Pro Asn Asn Ser Leu Val Ala Lys Glu Thr His Pro Asp Ser
      100          105          110
Leu Arg Ala Ile Tyr Gly Thr Asp Asp Leu Arg Asn Ala Leu His Gly
      115          120          125
Ser Asn Asp Phe Ala Ala Ala Glu Arg Glu Ile Arg Phe Met Phe Pro
      130          135          140
Glu Val Ile Val Glu Pro Ile Pro Ile Gly Gln Ala Ala Lys Asp Tyr
      145          150          155          160
Leu Asn Leu His Ile Met Pro Thr Leu Leu Glu Gly Leu Thr Glu Leu
      165          170          175
Cys Lys Gln Lys Pro Ala Asp Pro Leu Ile Trp Leu Ala Asp Trp Leu
      180          185          190
Leu Lys Asn Asn Pro Asn Lys Pro Lys Leu Cys His His Pro Ile Val
      195          200          205
Glu Glu Pro Tyr

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210

<210> 224
 <211> 3463
 <212> DNA
 <213> Homo sapiens

<400> 224

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<210> 225

<211> 495

<212> PRT

<213> Homo sapiens

<400> 225

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          20          25          30
Pro Arg Asp Arg Trp Met Phe Trp Ala Met Leu Pro Pro Pro Pro
          35          40          45
Pro Leu Thr Ser Ser Leu Pro Ala Ala Gly Ser Lys Pro Ser Ser Glu
          50          55          60
Ser Gln Pro Pro Met Glu Ala Gln Ser Leu Pro Gly Ala Pro Pro Pro
          65          70          75          80
Phe Asp Ala Gln Ile Leu Pro Gly Ala Gln Pro Pro Phe Asp Ala Gln
          85          90          95
Ser Pro Leu Asp Ser Gln Pro Gln Pro Ser Gly Gln Pro Trp Asn Phe
          100          105          110
His Ala Ser Thr Ser Trp Tyr Trp Arg Gln Ser Ser Asp Arg Phe Pro
          115          120          125
Arg His Gln Lys Ser Phe Asn Pro Ala Val Lys Asn Ser Tyr Tyr Pro
          130          135          140
Arg Lys Tyr Asp Ala Lys Phe Thr Asp Phe Ser Leu Pro Pro Ser Arg
          145          150          155          160
Lys Gln Lys Lys Lys Lys Arg Lys Glu Pro Val Phe His Phe Phe Cys
          165          170          175
Asp Thr Cys Asp Arg Gly Phe Lys Asn Gln Glu Lys Tyr Asp Lys His
          180          185          190
Met Ser Glu His Thr Lys Cys Pro Glu Leu Asp Cys Ser Phe Thr Ala
          195          200          205
His Glu Lys Ile Val Gln Phe His Trp Arg Asn Met His Ala Pro Gly
          210          215          220
Met Lys Lys Ile Lys Leu Asp Thr Pro Glu Glu Ile Ala Arg Trp Arg
          225          230          235          240
Glu Glu Arg Arg Lys Asn Tyr Pro Thr Leu Ala Asn Ile Glu Arg Lys
          245          250          255
Lys Lys Leu Lys Leu Glu Lys Glu Lys Arg Gly Ala Val Leu Thr Thr
          260          265          270
Thr Gln Tyr Gly Lys Met Lys Gly Met Ser Arg His Ser Gln Met Ala
          275          280          285
Lys Ile Arg Ser Pro Gly Lys Asn His Lys Trp Lys Asn Asp Asn Ser
          290          295          300
Arg Gln Arg Ala Val Thr Gly Ser Gly Ser His Leu Cys Asp Leu Lys
          305          310          315          320
Leu Glu Gly Pro Pro Glu Ala Asn Ala Asp Pro Leu Gly Val Leu Ile
          325          330          335

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244

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Asn Ser Asp Ser Glu Ser Asp Lys Glu Glu Lys Pro Gln His Ser Val
      340                      345                      350
Ile Pro Lys Glu Val Thr Pro Ala Leu Cys Ser Leu Met Ser Ser Tyr
      355                      360                      365
Gly Ser Leu Ser Gly Ser Glu Ser Glu Pro Glu Glu Thr Pro Ile Lys
      370                      375                      380
Thr Glu Ala Asp Val Leu Ala Glu Asn Gln Val Leu Asp Ser Ser Ala
385                      390                      395                      400
Pro Lys Ser Pro Ser Gln Asp Val Lys Ala Thr Val Arg Asn Phe Ser
      405                      410                      415
Glu Ala Lys Ser Glu Asn Arg Lys Lys Ser Phe Glu Lys Thr Asn Pro
      420                      425                      430
Lys Arg Lys Lys Asp Tyr His Asn Tyr Gln Thr Leu Phe Glu Pro Arg
      435                      440                      445
Thr His His Pro Tyr Leu Leu Glu Met Leu Leu Ala Pro Asp Ile Arg
      450                      455                      460
His Glu Arg Asn Val Ile Leu Gln Cys Val Arg Tyr Ile Ile Lys Lys
465                      470                      475                      480
Asp Phe Phe Gly Leu Asp Thr Asn Ser Ala Lys Ser Lys Asp Val
      485                      490                      495

```

<210> 226
 <211> 942
 <212> DNA
 <213> Homo sapiens

<400> 226
 atgagaattg cagtgatttg cttttgcctc ctaggcatca cctgtgccat accagttaaa 60
 caggctgatt ctggaagttc tgaggaaaag cagctttaca acaaataccc agatgctgtg 120
 gccacatggc taaacctcga cccatctcag aagcagaatc tcctagcccc acagaatgct 180
 gtgtcctctg aagaaaccaa tgactttaaa caagagaccc ttccaagtaa gtccaacgaa 240
 agccatgacc acatggatga tatggatgat gaagatgatg atgaccatgt ggacagccag 300
 gactccattg actcgaacga ctctgatgat gtagatgaca ctgatgattc tcaccagtct 360
 gatgagtctc accattctga tgaatctgat gaactggtca ctgattttcc caccggacctg 420
 ccagcaaccg aagttttcac tccagttgtc cccacagtag acacatatga tggccgaggt 480
 gatagtgtgg tttatggact gaggtcaaaa tctaagaagt ttgcgagacc tgacatccag 540
 taccctgatg ctacagacga gcacatcacc tcacacatgg aaagcgagga gttgaatggt 600
 gcatacaagg ccatccccgt tgcccaggac ctgaacgcgc cttctgattg ggacagccgt 660
 gggaaggaca gttatgaaac gagtcagctg gatgaccaga gtgctgaagc ccacagccac 720
 aagcagtcca gattatataa gcggaaagct aatgatgaga gcaatgagca ttccgatgtg 780
 attgatagtc aggaactttc caaagtcagc cgtgaattcc acagccatga atttcacagc 840
 catgaagata tgctggttgt agaccccaaa agtaaggaag aagataaaca cctgaaattt 900
 cgtattttctc atgaattaga tagtgcatct tctgaggtca at 942

<210> 227
 <211> 314
 <212> PRT
 <213> Homo sapiens

<400> 227
 Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
 1 5 10 15
 Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
 20 25 30
 Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
 35 40 45
 Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Asn Ala Val Ser Ser Glu

245

50	55	60
Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro Ser Lys Ser Asn Glu		
65	70	75
Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp Asp His		80
	85	90
Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp Asp Val Asp		95
	100	105
Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser Asp Glu		110
	115	120
Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala Thr Glu		125
	130	135
Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly Arg Gly		140
145	150	155
Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe Arg Arg		160
	165	170
Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu His Ile Thr Ser His		175
	180	185
Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro Val Ala		190
	195	200
Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys Asp Ser		205
	210	215
Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Ala His Ser His		220
225	230	235
Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser Asn Glu		240
	245	250
His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser Arg Glu		255
	260	265
Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val Val Asp		270
	275	280
Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile Ser His		285
	290	295
Glu Leu Asp Ser Ala Ser Ser Glu Val Asn		300
305	310	

<210> 228

<211> 1524

<212> DNA

<213> Homo sapiens

<400> 228

gcagagcaca	gcatcgtcgg	gaccagactc	gtctcaggcc	agttgcagcc	ttctcagcca	60
aacgccgacc	aaggaaaact	cactaccatg	agaattgcag	tgatttgctt	ttgcctccta	120
ggcatcacct	gtgccatacc	agttaaacag	gctgattctg	gaagttctga	ggaaaagcag	180
ctttacaaca	aatacccaga	tgctgtggcc	acatggctaa	accctgaccc	atctcagaag	240
cagaatctcc	tagccccaca	gacccttcca	agtaagtcca	acgaaagcca	tgaccacatg	300
gatgatatgg	atgatgaaga	tgatgatgac	catgtggaca	gccaggactc	cattgactcg	360
aacgactctg	atgatgtaga	tgacactgat	gattctcacc	agtctgatga	gtctcaccat	420
tctgatgaat	ctgatgaact	ggtcactgat	tttcccacgg	acctgccagc	aaccgaagtt	480
ttcactccag	ttgtccccac	agtagacaca	tatgatggcc	gaggtgatag	tgtggtttat	540
ggactgaggt	caaaatctaa	gaagtttcgc	agacctgaca	tccagtaccc	tgatgctaca	600
gacgaggaca	tcacctcaca	catggaaage	gaggagttag	atggtgcata	caaggccatc	660
cccgttgccc	aggacctgaa	cgcgccttct	gattgggaca	gccgtgggaa	ggacagttat	720
gaaacgagtc	agctggatga	ccagagtgtc	gaaaccacaa	gccacaagca	gtccagatta	780
tataagcggg	aagccaatga	tgagagcaat	gagcattccg	atgtgattga	tagtcaggaa	840
ctttccaaag	tcagccgtga	attccacagc	catgaatttc	acagccatga	agatatgctg	900
gtttagtagc	ccaaaagtaa	ggaagaagat	aaacacctga	aatttcgtat	ttctcatgaa	960
ttagatagtg	catcttctga	ggtcaattaa	aaggagaaaa	aatacaattt	ctcactttgc	1020

246

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atttagtcaa aagaaaaaat gctttatagc aaaatgaaag agaacatgaa atgcttcttt 1080
ctcagtttat tgggttgaatg tgtatctatt tgagtctgga aataactaat gtgtttgata 1140
attagtttag tttgtggctt catggaaaact ccctgtaaac taaaagcttc agggttatgt 1200
ctatgttcat tctatagaag aaatgcaaac tatcactgta ttttaatat ttgtattctc 1260
tcatgaatag aaatttatgt agaagcaaac aaaatacttt taccactta aaaagagaat 1320
ataacatttt atgtcactat aatcttttgt tttttaagtt agtgtatatt ttgttgtgat 1380
tatctttttg tgggtgtgaat aaatctttta tcttgaatgt aataagaatt tgggtggtgc 1440
aattgcttat ttgttttccc acggttgtcc agcaattaat aaaacataac cttttttact 1500
gcctaaaaaa aaaaaaaaaa aaaa                                     1524

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<210> 229

<211> 300

<212> PRT

<213> Homo sapiens

<400> 229

```

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
 1           5           10           15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu
          20           25           30
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro
          35           40           45
Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser
          50           55           60
Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp
65           70           75           80
Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp
          85           90           95
Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser
          100          105          110
Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala
          115          120          125
Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly
          130          135          140
Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe
145          150          155          160
Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr
          165          170          175
Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro
          180          185          190
Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys
          195          200          205
Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His
210          215          220
Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser
225          230          235          240
Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser
          245          250          255
Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val
          260          265          270
Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile
          275          280          285
Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
290          295          300

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<210> 230

<211> 861

<212> DNA

<213> Homo sapiens

<400> 230

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atgagaattg cagtgatttg cttttgcctc ctaggcatca cctgtgccat accagttaaa 60
caggctgatt ctggaagttc tgaggaaaag cagaatgctg tgcctctga agaaaccaat 120
gactttaaac aagagacctt tccaagtaag tccaacgaaa gccatgacca catggatgat 180
atggatgatg aagatgatga tgaccatgtg gacagccagg actccattga ctggaacgac 240
tctgatgatg tagatgacac tgatgattct caccagtctg atgagtctca ccattctgat 300
gaatctgatg aactgggtcac tgattttccc acggacctgc cagcaaccga agttttcact 360
ccagttgtcc ccacagtaga cacatatgat ggccgagggtg atagtgtggt ttatggactg 420
aggtcaaaat ctaagaagtt tcgcagacct gacatccagt accctgatgc tacagacgag 480
cacatcacct cacacatgga aagcgaggag ttgaatgggtg catacaaggc catccccgtt 540
gccaggacc tgaacgcgcc ttctgattgg gacagccgtg ggaaggacag ttatgaaacg 600
agtcagctgg atgaccagag tgctgaagcc cacagccaca agcagtccag attatataag 660
cggaaagcta atgatgagag caatgagcat tccgatgtga ttgatagtca ggaactttcc 720
aaagtcagcc gtgaattcca cagccatgaa ttacacagcc atgaagatat gctggttgta 780
gaccccaaaa gtaaggaaga agataaacac ctgaaatttc gtattttctca tgaattagat 840
agtcgatctt ctgaggtcaa t                                     861

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<210> 231

<211> 287

<212> PRT

<213> Homo sapiens

<400> 231

```

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala
 1           5           10          15
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Asn
          20          25          30
Ala Val Ser Ser Glu Glu Thr Asn Asp Phe Lys Gln Glu Thr Leu Pro
          35          40          45
Ser Lys Ser Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu
          50          55          60
Asp Asp Asp Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp
65          70          75          80
Ser Asp Asp Val Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser
          85          90          95
His His Ser Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp
          100         105         110
Leu Pro Ala Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr
          115         120         125
Tyr Asp Gly Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser
          130         135         140
Lys Lys Phe Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu
          145         150         155         160
His Ile Thr Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys
          165         170         175
Ala Ile Pro Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser
          180         185         190
Arg Gly Lys Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala
          195         200         205
Glu Ala His Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn
          210         215         220
Asp Glu Ser Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser
          225         230         235         240
Lys Val Ser Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp
          245         250         255

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248

Met Leu Val Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys
 260 265 270
 Phe Arg Ile Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn
 275 280 285

<210> 232
 <211> 838
 <212> DNA
 <213> Homo sapiens

<400> 232
 ctcagagcca cccacagccg cagccatgct gtgcctcctg ctcaccctgg gcgtggccct 60
 ggtctgtggt gtcccggcca tggacatccc ccagaccaag caggacctgg agctcccaaa 120
 gttggcaggg acctggcact ccatggccat ggcgaccaac aacatctccc tcatggcgac 180
 actgaaggcc cctctgaggg tccacatcac ctactgttg cccacccccg aggacaacct 240
 ggagatcggt ctgcacagat gggagaacaa cagctgtgtt gagaagaagg tccttgagaga 300
 gaagactgag aatccaaaga agttcaagat caactatacg gtggcgaacg aggccacgct 360
 gctcgatact gactacgaca atttctgtt tctctgccta caggacacca ccacccccat 420
 ccagagcatg atgtgccagt acctggccag agtcttggtg gaggacgatg agatcatgca 480
 gggattcatc agggctttca ggcccctgcc caggcaccta tggacttgc tggacttgaa 540
 acagatggaa gagccgtgcc gtttctaggt gagctcctgc ctggtcctgc ctctgggctc 600
 acctccgcct ccaggaagac cagactccca cccttccaca cctccagagc agtgggactt 660
 cctctgccc tttcaaagaa taaccacagc tcagaagacg atgacgtggt catctgtgtc 720
 gccatccct tctgtctgca cacctgcacc acggccatgg ggaggctgct ccctgggggc 780
 agagtctctg gcagaggtta ttaataaacc cttggagcat gaaaaaaaaa aaaaaaaaaa 838

<210> 233
 <211> 180
 <212> PRT
 <213> Homo sapiens

<400> 233
 Met Leu Cys Leu Leu Leu Thr Leu Gly Val Ala Leu Val Cys Gly Val
 1 5 10 15
 Pro Ala Met Asp Ile Pro Gln Thr Lys Gln Asp Leu Glu Leu Pro Lys
 20 25 30
 Leu Ala Gly Thr Trp His Ser Met Ala Met Ala Thr Asn Asn Ile Ser
 35 40 45
 Leu Met Ala Thr Leu Lys Ala Pro Leu Arg Val His Ile Thr Ser Leu
 50 55 60
 Leu Pro Thr Pro Glu Asp Asn Leu Glu Ile Val Leu His Arg Trp Glu
 65 70 75 80
 Asn Asn Ser Cys Val Glu Lys Lys Val Leu Gly Glu Lys Thr Glu Asn
 85 90 95
 Pro Lys Lys Phe Lys Ile Asn Tyr Thr Val Ala Asn Glu Ala Thr Leu
 100 105 110
 Leu Asp Thr Asp Tyr Asp Asn Phe Leu Phe Leu Cys Leu Gln Asp Thr
 115 120 125
 Thr Thr Pro Ile Gln Ser Met Met Cys Gln Tyr Leu Ala Arg Val Leu
 130 135 140
 Val Glu Asp Asp Glu Ile Met Gln Gly Phe Ile Arg Ala Phe Arg Pro
 145 150 155 160
 Leu Pro Arg His Leu Trp Tyr Leu Leu Asp Leu Lys Gln Met Glu Glu
 165 170 175
 Pro Cys Arg Phe
 180

<210> 234
 <211> 851
 <212> DNA
 <213> Homo sapiens

<400> 234
 ggctccagag ctcagagcca cccacagccg cagccatgct gtgcctcctg ctcaccctgg 60
 gcgtggccct ggtctgttgt gtcccggcca tggacatccc ccagaccaag caggacctgg 120
 agctcccaaa gttggcaggg acctggcact ccatggccat ggcgaccaac aacatctccc 180
 tcatggcgac actgaaggcc cctctgaggg tccacatcac ctcaactgttg cccacccccg 240
 aggacaacct ggagatcggt ctgcacagat gggagaacaa cagctgtgtt gagaagaagg 300
 tccttgagaga gaagactgag aatccaaaga agttcaagat caactatacg gtggcgaacg 360
 aggccacgct gctcgatact gactacgaca atttcctgtt tctctgccta caggacacca 420
 ccacccccat ccagagcatg atgtgccagt acctggccag agtcctgggt gaggacgatg 480
 agatcatgca gggattcatc agggctttca ggcccctgcc caggcaccta tgggtacttg 540
 tggacttgaa acagatggaa gagccgtgcc gtttctaggt gagctcctgc ctggctcctgc 600
 ctctgggtg acctgtaaac ccaacagctc acctccgcct ccaggaagac cagactccca 660
 ccctccaca cctccagagc agtgggactt cctcctgccc tttcaaagaa taaccacagc 720
 tcagaagacg atgacgttgt catctgtgtc gccatcccct tcctgctgca cacctgcacc 780
 acggccatgg ggaggctgct ccctgggggc agagtctctg gcagagggtta ttaataaacc 840
 cttggagcat g 851

<210> 235
 <211> 811
 <212> DNA
 <213> Homo sapiens

<400> 235
 catccctctg gctccagagc tcagagccac ccacagccgc agccatgctg tgcctcctgc 60
 tcaccctggg cgtggccctg gtctgttgtg tcccggccat ggacatcccc cagaccaagc 120
 aggacctgga gctcccaaag ttggcagggg cctggcactc catggccatg gcgaccaaca 180
 acatctccct catggcgaca ctgaaggccc ctctgagggg ccacatcacc tcaactgttg 240
 ccacccccga ggacaacctg gagatcggtt tgcacagatg ggagaacaac agctgtgttg 300
 agaagaaggc ccttggagag aagactggga atccaaagaa gttcaagatc aactatacgg 360
 tggcgaacga ggccacgctg ctcgatactg actacgacaa tttcctgttt ctctgcctac 420
 aggacaccac ccccccatc cagagcatga tgtgccagta cctggccaga gtcctgggtg 480
 aggacgatga gatcatgcag ggattcatca gggctttcag gccctgccc aggcacctat 540
 ggtacttgct ggacttgaaa cagatggaag agccgtgccg tttctagctc acctccgcct 600
 ccaggaagac cagactccca ccctccaca cctccagagc agtgggactt cctcctgccc 660
 tttcaaagaa taaccacagc tcagaagacg atgacgttgt catctgtgtc gccatcccct 720
 tcctgctgca cacctgcacc attgccatgg ggaggctgct ccctgggggc agagtctctg 780
 gcagagggtta ttaataaacc cttggagcat g 811

<210> 236
 <211> 850
 <212> DNA
 <213> Homo sapiens

<400> 236
 catccctctg gctccagagc tcagagccac ccacagccgc agccatgctg tgcctcctgc 60
 tcaccctggg cgtggccctg gtctgttgtg tcccggccat ggacatcccc cagaccaagc 120
 aggacctgga gctcccaaag ttggcagggg cctggcactc catggccatg gcgaccaaca 180
 acatctccct catggcgaca ctgaaggccc ctctgagggg ccacatcacc tcaactgttg 240
 ccacccccga ggacaacctg gagatcggtt tgcacagatg ggagaacaac agctgtgttg 300
 agaagaaggc ccttggagag aagactgrga atccaaagaa gttcaagatc aactatacgg 360
 tggcgaacga ggccacgctg ctcgatactg actacgacaa tttcctgttt ctctgcctac 420
 aggacaccac ccccccatc cagagcatga tgtgccagta cctggccaga gtcctgggtg 480

250

```

aggacgatga gatcatgcag ggattcatca gggctttcag gcccctgccc aggcacctat 540
ggtaacttgct ggacttgaaa cagatggaag agccgtgccc tttctagtga cctgtaaacc 600
caacagctca cctccgcctc caggaagacc agactccac ccttccacac ctccagagca 660
gtgggaacttc ctccctgccct ttcaaagaat aaccacagct cagaagacga tgacgtggtc 720
atctgtgtcg ccatcccctt cctgctgcac acctgcacca cggccatggg gaggtgctc 780
cctgggggca gagtctctgg cagaggttat taataaacc ttggagcatg aaaaaaaaaa 840
aaaaaaaaaa                                     850

```

<210> 237

<211> 598

<212> DNA

<213> Homo sapiens

<400> 237

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catccctctg gctccagagc tcagagccac ccacagccgc agccatgctg tgcctcctgc 60
tcaccctggg cgtggccctg gtctgtggtg tcccggccat ggacatcccc cagaccaagc 120
aggacctgga gctcccaaag gacaccacca ccccatcca gagcatgatg tgccagtacc 180
tggccagagt cctggtggag gacgatgaga tcatgcaggg attcatcagg gctttcaggc 240
ccctgcccag gcacctatgg tacttgctgg acttgaaaca gatggaagag ccgtgccgtt 300
tctaggtgag ctccctgcctg gtcctgcctc ctgggtgacc tgtaaaccce acagctcacc 360
tccgcctcca ggaagaccag actcccaccc ttccacacct ccagagcagt gggacttcc 420
cctgcccttt caaagaataa ccacagctca gaagacgatg acgtggtcat ctgtgtcgcc 480
atcccccttc tgtgcacac ctgcaccacg gccatgggga ggctgctccc tgggggcaga 540
gtctctggca gaggttatta ataaaccctt ggagcatgaa aaaaaaaaaa aaaaaaaa 598

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<210> 238

<211> 86

<212> PRT

<213> Homo sapiens

<400> 238

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Met Leu Cys Leu Leu Leu Thr Leu Gly Val Ala Leu Val Cys Gly Val
 1             5             10             15
Pro Ala Met Asp Ile Pro Gln Thr Lys Gln Asp Leu Glu Leu Pro Lys
      20             25             30
Asp Thr Thr Thr Pro Ile Gln Ser Met Met Cys Gln Tyr Leu Ala Arg
      35             40             45
Val Leu Val Glu Asp Asp Glu Ile Met Gln Gly Phe Ile Arg Ala Phe
      50             55             60
Arg Pro Leu Pro Arg His Leu Trp Tyr Leu Leu Asp Leu Lys Gln Met
65             70             75             80
Glu Glu Pro Cys Arg Phe
      85

```

<210> 239

<211> 814

<212> DNA

<213> Homo sapiens

<400> 239

```

catccctctg gctccagagc tcagagccac ccacagccgc agccatgctg tgcctcctgc 60
tcaccctggg cgtggccctg gtctgtggtg tcccggccat ggacatcccc cagaccaagc 120
aggacctgga gacactgaag gccctctga gggctccacat cacctcactg ttgccacccc 180
ccgaggacaa cctggagatc gttctgcaca gatgggagaa caacagctgt gttgagaaga 240
aggtccttgg agagaagact grgaatccaa agaagttcaa gatcaactat acggtggcga 300
acgaggccac gctgctcgat actgactacg acaatttcct gtttctctgc ctacaggaca 360
ccaccacccc catccagagc atgatgtgcc agtacctggc cagagtccctg gtggaggacg 420

```

251

```

atgagatcat gcagggattc atcagggcct tcaggcccct gccagggcac ctatggtact 480
tgctggactt gaaacagatg gaagagccgt gccgtttcta ggtgagctcc tgcctggtcc 540
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<210> 240
 <211> 158
 <212> PRT
 <213> Homo sapiens

<400> 240

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Pro	Ala	Met	Asp	Ile	Pro	Gln	Thr	Lys	Gln	Asp	Leu	Glu	Leu	Pro	Lys
			20					25					30		
Ala	Pro	Leu	Arg	Val	His	Ile	Thr	Ser	Leu	Leu	Pro	Thr	Pro	Glu	Asp
			35				40					45			
Asn	Leu	Glu	Ile	Val	Leu	His	Arg	Trp	Glu	Asn	Asn	Ser	Cys	Val	Glu
			50				55				60				
Lys	Lys	Val	Leu	Gly	Glu	Lys	Thr	Glu	Asn	Pro	Lys	Lys	Phe	Lys	Ile
65					70				75					80	
Asn	Tyr	Thr	Val	Ala	Asn	Glu	Ala	Thr	Leu	Leu	Asp	Thr	Asp	Tyr	Asp
			85					90						95	
Asn	Phe	Leu	Phe	Leu	Cys	Leu	Gln	Asp	Thr	Thr	Thr	Pro	Ile	Gln	Ser
			100				105						110		
Met	Met	Cys	Gln	Tyr	Leu	Ala	Arg	Val	Leu	Val	Glu	Asp	Asp	Glu	Ile
			115				120					125			
Met	Gln	Gly	Phe	Ile	Arg	Ala	Phe	Arg	Pro	Leu	Pro	Arg	His	Leu	Trp
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Tyr	Leu	Leu	Asp	Leu	Lys	Gln	Met	Glu	Glu	Pro	Cys	Arg	Phe		
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<210> 241
 <211> 158
 <212> PRT
 <213> Homo sapiens

<400> 241

Met	Leu	Cys	Leu	Leu	Leu	Thr	Leu	Gly	Val	Ala	Leu	Val	Cys	Gly	Val
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Pro	Ala	Met	Asp	Ile	Pro	Gln	Thr	Lys	Gln	Asp	Leu	Glu	Thr	Leu	Lys
			20					25					30		
Ala	Pro	Leu	Arg	Val	His	Ile	Thr	Ser	Leu	Leu	Pro	Thr	Pro	Glu	Asp
			35				40					45			
Asn	Leu	Glu	Ile	Val	Leu	His	Arg	Trp	Glu	Asn	Asn	Ser	Cys	Val	Glu
			50				55				60				
Lys	Lys	Val	Leu	Gly	Glu	Lys	Thr	Glu	Asn	Pro	Lys	Lys	Phe	Lys	Ile
65					70				75					80	
Asn	Tyr	Thr	Val	Ala	Asn	Glu	Ala	Thr	Leu	Leu	Asp	Thr	Asp	Tyr	Asp
			85					90					95		
Asn	Phe	Leu	Phe	Leu	Cys	Leu	Gln	Asp	Thr	Thr	Thr	Pro	Ile	Gln	Ser
			100				105					110			
Met	Met	Cys	Gln	Tyr	Leu	Ala	Arg	Val	Leu	Val	Glu	Asp	Asp	Glu	Ile
			115				120					125			

Met Gln Gly Phe Ile Arg Ala Phe Arg Pro Leu Pro Arg His Leu Trp
 130 135 140
 Tyr Leu Leu Asp Leu Lys Gln Met Glu Glu Pro Cys Arg Phe
 145 150 155

<210> 242
 <211> 2707
 <212> DNA
 <213> Homo sapiens

<400> 242
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 ggaggaagcc ccgagccctc ggccggctgc gagcgactcc ccggcgatgc ctccacaactc 180
 catcagatct ggccatggag ggctgaacca gctgggaggg gcctttgtga atggcagacc 240
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 ccccaaggtg gtggagaaga ttggggacta caaacgccag aacctacca tgtttgcctg 480
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<210> 243

<211> 450

<212> PRT

<213> Homo sapiens

<400> 243

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          20          25          30
Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser
          35          40          45
Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
          50          55          60
Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
65          70          75          80
Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
          85          90          95
Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu
          100          105          110
Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile
          115          120          125
Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met
          130          135          140
Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile
145          150          155          160
Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu
          165          170          175
Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly
          180          185          190
Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu
          195          200          205
Ser Ile Asp Ser Gln Ser Ser Ser Ser Gly Pro Arg Lys His Leu Arg
          210          215          220
Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe
225          230          235          240
Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys
          245          250          255
Gly Glu Gln Gly Leu Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp
          260          265          270
Asp Gly Lys Ala Thr Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn
          275          280          285
Leu Ser Thr His Gln Thr Tyr Pro Val Val Ala Asp Pro His Ser Pro
          290          295          300
Phe Ala Ile Lys Gln Glu Thr Pro Glu Val Ser Ser Ser Ser Ser Thr
305          310          315          320
Pro Ser Ser Leu Ser Ser Ser Ala Phe Leu Asp Leu Gln Gln Val Gly
          325          330          335
Ser Gly Val Pro Pro Phe Asn Ala Phe Pro His Ala Ala Ser Val Tyr
          340          345          350
Gly Gln Phe Thr Gly Gln Ala Leu Leu Ser Gly Arg Glu Met Val Gly
          355          360          365
Pro Thr Leu Pro Gly Tyr Pro Pro His Ile Pro Thr Ser Gly Gln Gly
          370          375          380
Ser Tyr Ala Ser Ser Ala Ile Ala Gly Met Val Ala Gly Ser Glu Tyr
385          390          395          400
Ser Gly Asn Ala Tyr Gly His Thr Pro Tyr Ser Ser Tyr Ser Glu Ala

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254

				405						410					415
Trp	Arg	Phe	Pro	Asn	Ser	Ser	Leu	Leu	Ser	Ser	Pro	Tyr	Tyr	Tyr	Ser
			420						425				430		
Ser	Thr	Ser	Arg	Pro	Ser	Ala	Pro	Pro	Thr	Thr	Ala	Thr	Ala	Phe	Asp
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His	Leu														
	450														

<210> 244

<211> 2381

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(2381)

<223> n = A,T,C or G

<400> 244

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255

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<210> 245

<211> 387

<212> PRT

<213> Homo sapiens

<400> 245

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Arg	Ile	Val	Asp	Leu	Ala	His	Gln	Gly	Val	Arg	Pro	Cys	Asp	Ile	Ser	35	40	45	
Arg	Gln	Leu	Arg	Val	Ser	His	Gly	Cys	Val	Ser	Lys	Ile	Leu	Gly	Arg	50	55	60	
Tyr	Tyr	Glu	Thr	Gly	Ser	Ile	Arg	Pro	Gly	Val	Ile	Gly	Gly	Ser	Lys	65	70	75	80
Pro	Lys	Val	Ala	Thr	Pro	Lys	Val	Val	Glu	Lys	Ile	Gly	Asp	Tyr	Lys	85	90	95	
Arg	Gln	Asn	Pro	Thr	Met	Phe	Ala	Trp	Glu	Ile	Arg	Asp	Arg	Leu	Leu	100	105	110	
Ala	Glu	Gly	Val	Cys	Asp	Asn	Asp	Thr	Val	Pro	Ser	Val	Ser	Ser	Ile	115	120	125	
Asn	Arg	Ile	Ile	Arg	Thr	Lys	Val	Gln	Gln	Pro	Phe	Asn	Leu	Pro	Met	130	135	140	
Asp	Ser	Cys	Val	Ala	Thr	Lys	Ser	Leu	Ser	Pro	Gly	His	Thr	Leu	Ile	145	150	155	160
Pro	Ser	Ser	Ala	Val	Thr	Pro	Pro	Glu	Ser	Pro	Gln	Ser	Asp	Ser	Leu	165	170	175	
Gly	Ser	Thr	Tyr	Ser	Ile	Asn	Gly	Leu	Leu	Gly	Ile	Ala	Gln	Pro	Gly	180	185	190	
Ser	Asp	Lys	Arg	Lys	Met	Asp	Asp	Ser	Asp	Gln	Asp	Ser	Cys	Arg	Leu	195	200	205	
Ser	Ile	Asp	Ser	Gln	Ser	Ser	Ser	Ser	Gly	Pro	Arg	Lys	His	Leu	Arg	210	215	220	
Thr	Asp	Ala	Phe	Ser	Gln	His	His	Leu	Glu	Pro	Leu	Glu	Cys	Pro	Phe	225	230	235	240
Glu	Arg	Gln	His	Tyr	Pro	Glu	Ala	Tyr	Ala	Ser	Pro	Ser	His	Thr	Lys	245	250	255	
Gly	Glu	Gln	Gly	Leu	Tyr	Pro	Leu	Pro	Leu	Leu	Asn	Ser	Thr	Leu	Asp	260	265	270	
Asp	Gly	Lys	Ala	Thr	Leu	Thr	Pro	Ser	Asn	Thr	Pro	Leu	Gly	Arg	Asn	275	280	285	
Leu	Ser	Thr	His	Gln	Thr	Tyr	Pro	Val	Val	Ala	Gly	Arg	Glu	Met	Val	290	295	300	
Gly	Pro	Thr	Leu	Pro	Gly	Tyr	Pro	Pro	His	Ile	Pro	Thr	Ser	Gly	Gln	305	310	315	320
Gly	Ser	Tyr	Ala	Ser	Ser	Ala	Ile	Ala	Gly	Met	Val	Ala	Gly	Ser	Glu	325	330	335	
Tyr	Ser	Gly	Asn	Ala	Tyr	Gly	His	Thr	Pro	Tyr	Ser	Ser	Tyr	Ser	Glu	340	345	350	
Ala	Trp	Arg	Phe	Pro	Asn	Ser	Ser	Leu	Leu	Ser	Ser	Pro	Tyr	Tyr	Tyr	355	360	365	
Ser	Ser	Thr	Ser	Arg	Pro	Ser	Ala	Pro	Pro	Thr	Thr	Ala	Thr	Ala	Phe	370	375	380	
Asp	His	Leu																	

385

<210> 246

<211> 387

<212> PRT

<213> Homo sapiens

<400> 246

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          20           25           30
Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser
          35           40           45
Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
          50           55           60
Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
65           70           75           80
Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
          85           90           95
Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu
          100          105          110
Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile
          115          120          125
Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met
          130          135          140
Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile
145          150          155          160
Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu
          165          170          175
Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly
          180          185          190
Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu
          195          200          205
Ser Ile Asp Ser Gln Ser Ser Ser Ser Gly Pro Arg Lys His Leu Arg
          210          215          220
Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe
225          230          235          240
Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys
          245          250          255
Gly Glu Gln Gly Leu Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp
          260          265          270
Asp Gly Lys Ala Thr Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn
          275          280          285
Leu Ser Thr His Gln Thr Tyr Pro Val Val Ala Gly Arg Glu Met Val
          290          295          300
Gly Pro Thr Leu Pro Gly Tyr Pro Pro His Ile Pro Thr Ser Gly Gln
305          310          315          320
Gly Ser Tyr Ala Ser Ser Ala Ile Ala Gly Met Val Ala Gly Ser Glu
          325          330          335
Tyr Ser Gly Asn Ala Tyr Gly His Thr Pro Tyr Ser Ser Tyr Ser Glu
          340          345          350
Ala Trp Gly Phe Pro Asn Ser Ser Leu Leu Ser Ser Pro Tyr Tyr Tyr
          355          360          365
Ser Ser Thr Ser Arg Pro Ser Ala Pro Pro Thr Thr Ala Thr Ala Phe
          370          375          380
Asp His Leu

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385

<210> 247
 <211> 2641
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(2641)
 <223> n = A,T,C or G

<400> 247
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 gccctgtggg gcttctctcc ttgatgcttc tttctttttt taaagacaac ctgccattac 2580
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258

a

2641

<210> 248

<211> 398

<212> PRT

<213> Homo sapiens

<400> 248

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      20      25      30
Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser
      35      40      45
Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
      50      55      60
Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
65      70      75      80
Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
      85      90      95
Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu
      100      105      110
Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile
      115      120      125
Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met
130      135      140
Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile
145      150      155      160
Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu
      165      170      175
Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly
      180      185      190
Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu
195      200      205
Ser Ile Asp Ser Gln Ser Ser Ser Ser Gly Pro Arg Lys His Leu Arg
210      215      220
Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe
225      230      235      240
Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys
      245      250      255
Gly Glu Gln Gly Leu Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp
260      265      270
Asp Gly Lys Ala Thr Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn
275      280      285
Leu Ser Thr His Gln Thr Tyr Pro Val Val Ala Ala Pro Pro Phe Trp
290      295      300
Ile Cys Ser Lys Ser Ala Pro Gly Ser Arg Pro Ser Met Pro Phe Pro
305      310      315      320
Met Leu Pro Pro Cys Thr Gly Ser Ser Arg Ala Arg Pro Ser Ser Gln
      325      330      335
Gly Glu Arg Trp Trp Gly Pro Arg Cys Pro Asp Thr His Pro Thr Ser
340      345      350
Pro Pro Ala Asp Arg Ala Ala Met Pro Pro Leu Pro Ser Gln Ala Trp
355      360      365
Trp Gln Glu Val Asn Thr Leu Ala Met Pro Met Ala Thr Pro Pro Thr
370      375      380
Pro Pro Thr Ala Arg Pro Gly Ala Ser Pro Thr Pro Ala Cys
385      390      395

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<210> 249
 <211> 2410
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(2410)
 <223> n = A,T,C or G

<400> 249
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 ccgagaccgg ctccctggctg agggcgctctg tgacaatgac actgtgcccc gtgtcagctc 540
 cattaataga atcatccgga ccaaagtgcg gcaaccattc aacctcccta tggacagctg 600
 cgtggccacc aagtccctga gtcccgga caacgctgat cccagctcag ctgtaactcc 660
 cccggagtca cccagtcgg attccctggg ctccacctac tccatcaatg ggctcctggg 720
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 gggaggtgag gtgtgggtgt cggcttcacc cagggcagaa caaggcagaa tcgcaggaaa 2040
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 tctctctttg cctgtgggg cttctctcct tgatgcttct ttctttttt aaagacaacc 2340
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<210> 250
 <211> 321
 <212> PRT

<213> Homo sapiens

<400> 250

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Met Pro His Asn Ser Ile Arg Ser Gly His Gly Gly Leu Asn Gln Leu
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Gly Gly Ala Phe Val Asn Gly Arg Pro Leu Pro Glu Val Val Arg Gln
          20           25           30
Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser
      35           40           45
Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
    50           55           60
Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
65           70           75           80
Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
          85           90           95
Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu
          100          105          110
Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile
          115          120          125
Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met
    130          135          140
Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile
145          150          155          160
Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu
          165          170          175
Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly
      180          185          190
Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu
    195          200          205
Ser Ile Asp Ser Gln Ser Ser Ser Ser Gly Pro Arg Lys His Leu Arg
    210          215          220
Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe
225          230          235          240
Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys
          245          250          255
Gly Glu Gln Gly Glu Arg Trp Trp Gly Pro Arg Cys Pro Asp Thr His
          260          265          270
Pro Thr Ser Pro Pro Ala Asp Arg Ala Ala Met Pro Pro Leu Pro Ser
    275          280          285
Gln Ala Trp Trp Gln Glu Val Asn Thr Leu Ala Met Pro Met Ala Thr
    290          295          300
Pro Pro Thr Pro Pro Thr Ala Arg Pro Gly Ala Ser Pro Thr Pro Ala
305          310          315          320
Cys

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<210> 251

<211> 2308

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(2308)

<223> n = A,T,C or G

<400> 251


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cattaataga atcatccgga ccaaagtga gcaaccattc aacctcccta tggacagctg 600
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cccggagtca cccagtcgg attccctggg ctccacctac tccatcaatg ggctcctggg 720
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tggcctctga gtgaaatgtc tctctttgcc ctgtggggt tctctccttg atgttcttt 2220
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aaaaaaaaa aaaaaaaaaa aaaaaaaaaa 2308

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<210> 252

<211> 287

<212> PRT

<213> Homo sapiens

<400> 252

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Met Pro His Asn Ser Ile Arg Ser Gly His Gly Gly Leu Asn Gln Leu
1           5           10           15
Gly Gly Ala Phe Val Asn Gly Arg Pro Leu Pro Glu Val Val Arg Gln
20           25           30
Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser
35           40           45
Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg
50           55           60
Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys
65           70           75           80
Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys
85           90           95

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262

Arg	Gln	Asn	Pro	Thr	Met	Phe	Ala	Trp	Glu	Ile	Arg	Asp	Arg	Leu	Leu
		100						105					110		
Ala	Glu	Gly	Val	Cys	Asp	Asn	Asp	Thr	Val	Pro	Ser	Val	Ser	Ser	Ile
		115					120					125			
Asn	Arg	Ile	Ile	Arg	Thr	Lys	Val	Gln	Gln	Pro	Phe	Asn	Leu	Pro	Met
	130					135					140				
Asp	Ser	Cys	Val	Ala	Thr	Lys	Ser	Leu	Ser	Pro	Gly	His	Thr	Leu	Ile
	145					150				155					160
Pro	Ser	Ser	Ala	Val	Thr	Pro	Pro	Glu	Ser	Pro	Gln	Ser	Asp	Ser	Leu
			165						170					175	
Gly	Ser	Thr	Tyr	Ser	Ile	Asn	Gly	Leu	Leu	Gly	Ile	Ala	Gln	Pro	Gly
			180					185					190		
Ser	Asp	Lys	Arg	Lys	Met	Asp	Asp	Ser	Asp	Gln	Asp	Ser	Cys	Arg	Leu
	195						200					205			
Ser	Ile	Asp	Ser	Gln	Ser	Ser	Ser	Ser	Gly	Pro	Arg	Lys	His	Leu	Arg
	210					215					220				
Thr	Asp	Ala	Phe	Ser	Gln	His	His	Leu	Glu	Pro	Leu	Glu	Cys	Pro	Phe
	225					230				235					240
Glu	Arg	Gln	His	Tyr	Pro	Glu	Ala	Tyr	Ala	Ser	Pro	Ser	His	Thr	Lys
			245					250						255	
Gly	Glu	Gln	Glu	Val	Asn	Thr	Leu	Ala	Met	Pro	Met	Ala	Thr	Pro	Pro
		260						265					270		
Thr	Pro	Pro	Thr	Ala	Arg	Pro	Gly	Ala	Ser	Pro	Thr	Pro	Ala	Cys	
		275					280					285			

<210> 253

<211> 2148

<212> DNA

<213> Homo sapiens

<400> 253

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actctctgag gaaaaacat tttgattatt actctcagac gtgctgtggca acaagtgact 180
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263

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tgtccccctg gagagttatg aggacatcca tggtagccctc cacctggaga ggcttgcccta 1620
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<210> 254

<211> 509

<212> PRT

<213> Homo sapiens

<400> 254

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Met Glu Arg Arg Arg Leu Trp Gly Ser Ile Gln Ser Arg Tyr Ile Ser
 1          5          10          15
Met Ser Val Trp Thr Ser Pro Arg Arg Leu Val Glu Leu Ala Gly Gln
 20          25          30
Ser Leu Leu Lys Asp Glu Ala Leu Ala Ile Ala Ala Leu Glu Leu Leu
 35          40          45
Pro Arg Glu Leu Phe Pro Pro Leu Phe Met Ala Ala Phe Asp Gly Arg
 50          55          60
His Ser Gln Thr Leu Lys Ala Met Val Gln Ala Trp Pro Phe Thr Cys
 65          70          75          80
Leu Pro Leu Gly Val Leu Met Lys Gly Gln His Leu His Leu Glu Thr
 85          90          95
Phe Lys Ala Val Leu Asp Gly Leu Asp Val Leu Leu Ala Gln Glu Val
100          105          110
Arg Pro Arg Arg Trp Lys Leu Gln Val Leu Asp Leu Arg Lys Asn Ser
115          120          125
His Gln Asp Phe Trp Thr Val Trp Ser Gly Asn Arg Ala Ser Leu Tyr
130          135          140
Ser Phe Pro Glu Pro Glu Ala Ala Gln Pro Met Thr Lys Lys Arg Lys
145          150          155          160
Val Asp Gly Leu Ser Thr Glu Ala Glu Gln Pro Phe Ile Pro Val Glu
165          170          175
Val Leu Val Asp Leu Phe Leu Lys Glu Gly Ala Cys Asp Glu Leu Phe
180          185          190
Ser Tyr Leu Ile Glu Lys Val Lys Arg Lys Lys Asn Val Leu Arg Leu
195          200          205
Cys Cys Lys Lys Leu Lys Ile Phe Ala Met Pro Met Gln Asp Ile Lys
210          215          220
Met Ile Leu Lys Met Val Gln Leu Asp Ser Ile Glu Asp Leu Glu Val
225          230          235          240
Thr Cys Thr Trp Lys Leu Pro Thr Leu Ala Lys Phe Ser Pro Tyr Leu
245          250          255
Gly Gln Met Ile Asn Leu Arg Arg Leu Leu Leu Ser His Ile His Ala
260          265          270
Ser Ser Tyr Ile Ser Pro Glu Lys Glu Glu Gln Tyr Ile Ala Gln Phe
275          280          285
Thr Ser Gln Phe Leu Ser Leu Gln Cys Leu Gln Ala Leu Tyr Val Asp
290          295          300
Ser Leu Phe Phe Leu Arg Gly Arg Leu Asp Gln Leu Leu Arg His Val
305          310          315          320
Met Asn Pro Leu Glu Thr Leu Ser Ile Thr Asn Cys Arg Leu Ser Glu

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				325						330					335
Gly	Asp	Val	Met	His	Leu	Ser	Gln	Ser	Pro	Ser	Val	Ser	Gln	Leu	Ser
			340					345					350		
Val	Leu	Ser	Leu	Ser	Gly	Val	Met	Leu	Thr	Asp	Val	Ser	Pro	Glu	Pro
		355					360					365			
Leu	Gln	Ala	Leu	Leu	Glu	Arg	Ala	Ser	Ala	Thr	Leu	Gln	Asp	Leu	Val
	370					375						380			
Phe	Asp	Glu	Cys	Gly	Ile	Thr	Asp	Asp	Gln	Leu	Leu	Ala	Leu	Leu	Pro
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<211> 2261

<212> DNA

<213> Homo sapiens

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<212> PRT

<213> Homo sapiens

<400> 256

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 35          40          45
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Glu Gly Asp Pro Cys Thr Val Ser Ser Gln Leu Glu Leu Glu Glu Ala
 65          70          75          80
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 85          90          95
Phe Pro Cys Val Pro Glu Arg Pro Gly Met Pro Cys Pro Gly Glu Asp
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Cys Ala Ile Cys Thr Asp Arg Ile Trp Gly Leu Gly Arg Gln Gly Tyr
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Val Thr Ile Glu Cys Gly Arg His Ser Leu Pro Gln Glu Pro Val Met
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Pro Met Asp Gln Ser Ser Met His Ser Asp His Ala Gln Thr Val Ile
195          200          205
Pro Tyr Asn Pro Ser Ser His Glu Ser Leu Asp Gln Val Gly Glu Glu
210          215          220
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Ala Lys Val Leu Leu Val Arg Leu Lys Lys Thr Asp Arg Ile Tyr Ala
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Met Lys Val Val Lys Lys Glu Leu Val Asn Asp Asp Glu Asp Ile Asp
275          280          285
Trp Val Gln Thr Glu Lys His Val Phe Glu Gln Ala Ser Asn His Pro
290          295          300
Phe Leu Val Gly Leu His Ser Cys Phe Gln Thr Glu Ser Arg Leu Phe
305          310          315          320

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<212> DNA

<213> Homo sapiens

<400> 257

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<210> 258

<211> 1043

<212> PRT

<213> Homo sapiens

<400> 258

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35          40          45
Pro Glu Met Glu Asp Ala Asn Ser Glu Lys Ser Ile Asn Glu Glu Asn
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Gly Glu Val Ser Glu Asp Gln Ser Gln Asn Lys His Ser Arg His Lys
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Lys Lys Lys His Lys His Arg Ser Lys His Lys Lys His Lys His Ser
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<211> 1834

<212> DNA

<213> Homo sapiens

<400> 261

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 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Ser Ser Ala Val Ala Gly Gln Trp Pro Trp Gln Val Ser Ile Thr Tyr
 50 55 60
 Glu Gly Val His Val Cys Gly Gly Ser Leu Val Ser Glu Gln Trp Val
 65 70 75 80
 Leu Ser Ala Ala His Cys Phe Pro Ser Glu His His Lys Glu Ala Tyr
 85 90 95
 Glu Val Lys Leu Gly Ala His Gln Leu Asp Ser Tyr Ser Glu Asp Ala
 100 105 110
 Lys Val Ser Thr Leu Lys Asp Ile Ile Pro His Pro Ser Tyr Leu Gln
 115 120 125
 Glu Gly Ser Gln Gly Asp Ile Ala Leu Leu Gln Leu Ser Arg Pro Ile
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 Val Pro Leu Ile Ser Arg Glu Thr Cys Asn Cys Leu Tyr Asn Ile Asp
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 Gly Tyr Val Glu Gly Gly Lys Asp Ala Cys Gln Gly Asp Ser Gly Gly
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 Ser Trp Gly Asp Ala Cys Gly Ala Arg Asn Arg Pro Gly Val Tyr Thr
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<210> 264

<211> 599

<212> PRT

<213> Homo sapiens

<400> 264

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Asn Pro Cys Cys Tyr Tyr Pro Cys Gln His Gln Gly Ile Cys Val Arg
35         40         45
Phe Gly Leu Asp Arg Tyr Gln Cys Asp Cys Thr Arg Thr Gly Tyr Ser
50         55         60

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Gly	Pro	Asn	Cys	Thr	Ile	Pro	Gly	Leu	Trp	Thr	Trp	Leu	Arg	Asn	Ser	65	70	75	80
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Trp	Phe	Trp	Glu	Phe	Val	Asn	Ala	Thr	Phe	Ile	Arg	Glu	Met	Leu	Met	100	105	110	
Arg	Leu	Val	Leu	Thr	Val	Arg	Ser	Asn	Leu	Ile	Pro	Ser	Pro	Pro	Thr	115	120	125	
Tyr	Asn	Ser	Ala	His	Asp	Tyr	Ile	Ser	Trp	Glu	Ser	Phe	Ser	Asn	Val	130	135	140	
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Pro	Met	Gly	Thr	Lys	Gly	Lys	Lys	Gln	Leu	Pro	Asp	Ala	Gln	Leu	Leu	165	170	175	
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Tyr	Gln	Leu	Arg	Leu	Phe	Lys	Asp	Gly	Lys	Leu	Lys	Tyr	Gln	Val	Leu	245	250	255	
Asp	Gly	Glu	Met	Tyr	Pro	Pro	Ser	Val	Glu	Glu	Ala	Pro	Val	Leu	Met	260	265	270	
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Glu	Val	Phe	Gly	Leu	Leu	Pro	Gly	Leu	Met	Leu	Tyr	Ala	Thr	Leu	Trp	290	295	300	
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Gly	Glu	Thr	Ile	Lys	Ile	Val	Ile	Glu	Glu	Tyr	Val	Gln	Gln	Leu	Ser	340	345	350	
Gly	Tyr	Phe	Leu	Gln	Leu	Lys	Phe	Asp	Pro	Glu	Leu	Leu	Phe	Gly	Val	355	360	365	
Gln	Phe	Gln	Tyr	Arg	Asn	Arg	Ile	Ala	Met	Glu	Phe	Asn	His	Leu	Tyr	370	375	380	
His	Trp	His	Pro	Leu	Met	Pro	Asp	Ser	Phe	Lys	Val	Gly	Ser	Gln	Glu	385	390	395	400
Tyr	Ser	Tyr	Glu	Gln	Phe	Leu	Phe	Asn	Thr	Ser	Met	Leu	Val	Asp	Tyr	405	410	415	
Gly	Val	Glu	Ala	Leu	Val	Asp	Ala	Phe	Ser	Arg	Gln	Ile	Ala	Gly	Arg	420	425	430	
Ile	Gly	Gly	Gly	Arg	Asn	Met	Asp	His	His	Ile	Leu	His	Val	Ala	Val	435	440	445	
Asp	Val	Ile	Arg	Glu	Ser	Arg	Glu	Met	Arg	Leu	Gln	Pro	Phe	Asn	Glu	450	455	460	
Tyr	Arg	Lys	Arg	Phe	Gly	Met	Lys	Pro	Tyr	Thr	Ser	Phe	Gln	Glu	Leu	465	470	475	480
Val	Gly	Glu	Lys	Glu	Met	Ala	Ala	Glu	Leu	Glu	Glu	Leu	Tyr	Gly	Asp	485	490	495	
Ile	Asp	Ala	Leu	Glu	Phe	Tyr	Pro	Gly	Leu	Leu	Leu	Glu	Lys	Cys	His	500	505	510	
Pro	Asn	Ser	Ile	Phe	Gly	Glu	Ser	Met	Ile	Glu	Ile	Gly	Ala	Pro	Phe	515	520	525	

Ser Leu Lys Gly Leu Leu Gly Asn Pro Ile Cys Ser Pro Glu Tyr Trp
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 Lys Pro Ser Thr Phe Gly Gly Glu Val Gly Phe Asn Ile Val Lys Thr
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 Ala Thr Leu Lys Lys Leu Val Cys Leu Asn Thr Lys Thr Cys Pro Tyr
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 <211> 3000
 <212> DNA
 <213> Homo sapiens

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<211> 350

<212> PRT

<213> Homo sapiens

<400> 266

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      35           40           45
Trp Asp Lys Asp Tyr Asp Ser Phe Val Leu Pro Leu Leu Glu Asp Lys
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      65           70           75           80
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Val Ser Leu His Gly Tyr Lys Lys Tyr Leu Leu Ser Gln Ser Ser Pro
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Glu Val Gln Thr Asp Val Gly Val Asp Thr Lys His Gln Thr Leu Gln
      165          170          175
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      180          185          190
Leu Asn Asn Arg Gln Leu Asn Tyr Val Gln Leu Glu Ile Asp Ile Lys
      195          200          205
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      210          215          220
Leu Pro Lys Arg Ile Pro Lys Asp Ser Ala Arg Tyr His Phe Phe Leu
      225          230          235          240
Tyr Lys His Ser His Glu Gly Asp Tyr Leu Glu Ser Ile Val Phe Ile
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Tyr Ser Met Pro Gly Tyr Thr Cys Ser Ile Arg Glu Arg Met Leu Tyr
      260          265          270
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      275          280          285
Met Asp Val Ile Arg Lys Ile Glu Ile Asp Asn Gly Asp Glu Leu Thr
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Ala Asp Phe Leu Tyr Glu Glu Val His Pro Lys Gln His Ala His Lys
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280

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<210> 267
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 <212> DNA
 <213> Homo sapiens

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<210> 268
 <211> 103
 <212> PRT
 <213> Homo sapiens

<400> 268
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 1 5 10 15
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 20 25 30
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 35 40 45
 Thr Thr Gly Tyr Gly Gly Val Arg Ala Leu Cys Gly Trp Thr Pro Ser
 50 55 60
 Ser Gly Ala Thr Pro Arg Asn Arg Leu Leu Leu Gln Leu Leu Gly Ser
 65 70 75 80
 Pro Gly Arg Arg Tyr Tyr Ser Leu Pro Pro His Gln Lys Val Pro Leu
 85 90 95
 Pro Ser Leu Ser Pro Thr Met
 100

<210> 269
 <211> 607
 <212> DNA
 <213> Homo sapiens

<400> 269
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281

<210> 270
 <211> 94
 <212> PRT
 <213> Homo sapiens

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 20 25 30
 Glu Leu Lys Glu Leu Leu Gln Thr Glu Leu Ser Gly Phe Leu Asp Ala
 35 40 45
 Gln Lys Asp Val Asp Ala Val Asp Lys Val Met Lys Glu Leu Asp Glu
 50 55 60
 Asn Gly Asp Gly Glu Val Asp Phe Gln Glu Tyr Val Val Leu Val Ala
 65 70 75 80
 Ala Leu Thr Val Ala Cys Asn Asn Phe Phe Trp Glu Asn Ser
 85 90

<210> 271
 <211> 595
 <212> DNA
 <213> Homo sapiens

<400> 271
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<210> 272
 <211> 105
 <212> PRT
 <213> Homo sapiens

<400> 272
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 35 40 45
 Ala Phe Thr Lys Asn Gln Lys Asp Pro Gly Val Leu Asp Arg Met Met
 50 55 60
 Lys Lys Leu Asp Thr Asn Ser Asp Gly Gln Leu Asp Phe Ser Glu Phe
 65 70 75 80
 Leu Asn Leu Ile Gly Gly Leu Ala Met Ala Cys His Asp Ser Phe Leu
 85 90 95
 Lys Ala Val Pro Ser Gln Lys Arg Thr
 100 105

<210> 273
 <211> 428
 <212> DNA
 <213> Homo sapiens

<400> 273
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<210> 274
 <211> 97
 <212> PRT
 <213> Homo sapiens

<400> 274
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 20 25 30
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 35 40 45
 Lys Val Asp Glu Glu Gly Leu Lys Lys Leu Met Gly Ser Leu Asp Glu
 50 55 60
 Asn Ser Asp Gln Gln Val Asp Phe Gln Glu Tyr Ala Val Phe Leu Ala
 65 70 75 80
 Leu Ile Thr Val Met Cys Asn Asp Phe Phe Gln Gly Cys Pro Asp Arg
 85 90 95
 Pro

<210> 275
 <211> 470
 <212> DNA
 <213> Homo sapiens

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 gccctcaagg gctgaaaata aatagggaag atggagacac ctctgggggt cctctctgag 420
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<210> 276
 <211> 90
 <212> PRT
 <213> Homo sapiens

<400> 276

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 Glu Leu Lys Glu Leu Ile Gln Lys Glu Leu Thr Ile Gly Ser Lys Leu
 35 40 45
 Gln Asp Ala Glu Ile Ala Arg Leu Met Glu Asp Leu Asp Arg Asn Lys
 50 55 60
 Asp Gln Glu Val Asn Phe Gln Glu Tyr Val Thr Phe Leu Gly Ala Leu
 65 70 75 80
 Ala Leu Ile Tyr Asn Glu Ala Leu Lys Gly
 85 90

<210> 277

<211> 3151

<212> DNA

<213> Homo sapiens

<400> 277

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<210> 278

<211> 669

<212> PRT

<213> Homo sapiens

<400> 278

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Pro Glu Pro Ala Ala Pro Gln Gln Pro Thr Ala Glu Glu Glu Ala Leu
35           40           45
Ile Glu Phe His Arg Ser Tyr Arg Glu Leu Phe Glu Phe Phe Cys Asn
50           55           60
Asn Thr Thr Ile His Gly Ala Ile Arg Leu Val Cys Ser Gln His Asn
65           70           75           80
Arg Met Lys Thr Ala Phe Trp Ala Val Leu Trp Leu Cys Thr Phe Gly
85           90           95
Met Met Tyr Trp Gln Phe Gly Leu Leu Phe Gly Glu Tyr Phe Ser Tyr
100          105          110
Pro Val Ser Leu Asn Ile Asn Leu Asn Ser Asp Lys Leu Val Phe Pro
115          120          125
Ala Val Thr Ile Cys Thr Leu Asn Pro Tyr Arg Tyr Pro Glu Ile Lys
130          135          140
Glu Glu Leu Glu Glu Leu Asp Arg Ile Thr Glu Gln Thr Leu Phe Asp
145          150          155          160
Leu Tyr Lys Tyr Ser Ser Phe Thr Thr Leu Val Ala Gly Ser Arg Ser
165          170          175
Arg Arg Asp Leu Arg Gly Thr Leu Pro His Pro Leu Gln Arg Leu Arg
180          185          190
Val Pro Pro Pro Pro His Gly Ala Arg Arg Ala Arg Ser Val Ala Ser
195          200          205
Ser Leu Arg Asp Asn Asn Pro Gln Val Asp Trp Lys Asp Trp Lys Ile
210          215          220
Gly Phe Gln Leu Cys Asn Gln Asn Lys Ser Asp Cys Phe Tyr Gln Thr
225          230          235          240
Tyr Ser Ser Gly Val Asp Ala Val Arg Glu Trp Tyr Arg Phe His Tyr
245          250          255
Ile Asn Ile Leu Ser Arg Leu Pro Glu Thr Leu Pro Ser Leu Glu Glu
260          265          270

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285

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 Cys Asn Gln Ala Asn Tyr Ser His Phe His His Pro Met Tyr Gly Asn
 290 295 300
 Cys Tyr Thr Phe Asn Asp Lys Asn Asn Ser Asn Leu Trp Met Ser Ser
 305 310 315 320
 Met Pro Gly Ile Asn Asn Gly Leu Ser Leu Met Leu Arg Ala Glu Gln
 325 330 335
 Asn Asp Phe Ile Pro Leu Leu Ser Thr Val Thr Gly Ala Arg Val Met
 340 345 350
 Val His Gly Gln Asp Glu Pro Ala Phe Met Asp Asp Gly Gly Phe Asn
 355 360 365
 Leu Arg Pro Gly Val Glu Thr Ser Ile Ser Met Arg Lys Glu Thr Leu
 370 375 380
 Asp Arg Leu Gly Gly Asp Tyr Gly Asp Cys Thr Lys Asn Gly Ser Asp
 385 390 395 400
 Val Pro Val Glu Asn Leu Tyr Pro Ser Lys Tyr Thr Gln Gln Val Cys
 405 410 415
 Ile His Ser Cys Phe Gln Glu Ser Met Ile Lys Glu Cys Gly Cys Ala
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 Tyr Ile Phe Tyr Pro Arg Pro Gln Asn Val Glu Tyr Cys Asp Tyr Arg
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 Lys His Ser Ser Trp Gly Tyr Cys Tyr Tyr Lys Leu Gln Val Asp Phe
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 Ser Ser Asp His Leu Gly Cys Phe Thr Lys Cys Arg Lys Pro Cys Ser
 465 470 475 480
 Val Thr Ser Tyr Gln Leu Ser Ala Gly Tyr Ser Arg Trp Pro Ser Val
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 Lys Glu Leu Asn Tyr Lys Thr Asn Ser Glu Ser Pro Ser Val Thr Met
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 Val Thr Leu Leu Ser Asn Leu Gly Ser Gln Trp Ser Leu Trp Phe Gly
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 Trp Ser Pro Gly Arg Gly Gly Arg Gly Ala Gln Glu Val Ala Ser Thr
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 Ser Leu Ser Gln Pro Gly Pro Ala Pro Ser Pro Ala Leu Thr Ala Pro
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<210> 279

<211> 3174

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

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<223> n = A,T,C or G

<400> 279

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<210> 280
 <211> 669
 <212> PRT
 <213> Homo sapiens

<400> 280

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			20					25					30		
Pro	Glu	Pro	Ala	Ala	Pro	Gln	Gln	Pro	Thr	Ala	Glu	Glu	Glu	Ala	Leu
		35					40					45			
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65					70					75				80	
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				85				90						95	
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			100					105					110		
Pro	Val	Ser	Leu	Asn	Ile	Asn	Leu	Asn	Ser	Asp	Lys	Leu	Val	Phe	Pro
		115					120					125			
Ala	Val	Thr	Ile	Cys	Thr	Leu	Asn	Pro	Tyr	Arg	Tyr	Pro	Glu	Ile	Lys
	130					135					140				
Glu	Glu	Leu	Glu	Glu	Leu	Asp	Arg	Ile	Thr	Glu	Gln	Thr	Leu	Phe	Asp
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Leu	Tyr	Lys	Tyr	Ser	Ser	Phe	Thr	Thr	Leu	Val	Ala	Gly	Ser	Arg	Ser
				165				170						175	
Arg	Arg	Asp	Leu	Arg	Gly	Thr	Leu	Pro	His	Pro	Leu	Gln	Arg	Leu	Arg
			180					185					190		
Val	Pro	Pro	Pro	Pro	His	Gly	Ala	Arg	Arg	Ala	Arg	Ser	Val	Ala	Ser
		195					200					205			
Ser	Leu	Arg	Asp	Asn	Asn	Pro	Gln	Val	Asp	Trp	Lys	Asp	Trp	Lys	Ile
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Gly	Phe	Gln	Leu	Cys	Asn	Gln	Asn	Lys	Ser	Asp	Cys	Phe	Tyr	Gln	Thr
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Tyr	Ser	Ser	Gly	Val	Asp	Ala	Val	Arg	Glu	Trp	Tyr	Arg	Phe	His	Tyr
				245					250					255	
Ile	Asn	Ile	Leu	Ser	Arg	Leu	Pro	Glu	Thr	Leu	Pro	Ser	Leu	Glu	Glu
		260						265					270		
Asp	Thr	Leu	Gly	Asn	Phe	Ile	Phe	Ala	Cys	Arg	Phe	Asn	Gln	Val	Ser
	275						280					285			
Cys	Asn	Gln	Ala	Asn	Tyr	Ser	His	Phe	His	His	Pro	Met	Tyr	Gly	Asn
	290					295					300				
Cys	Tyr	Thr	Phe	Asn	Asp	Lys	Asn	Asn	Ser	Asn	Leu	Trp	Met	Ser	Ser
305					310					315				320	
Met	Pro	Gly	Ile	Asn	Asn	Gly	Leu	Ser	Leu	Met	Leu	Arg	Ala	Glu	Gln
				325					330					335	
Asn	Asp	Phe	Ile	Pro	Leu	Leu	Ser	Thr	Val	Thr	Gly	Ala	Arg	Val	Met
			340					345					350		
Val	His	Gly	Gln	Asp	Glu	Pro	Ala	Phe	Met	Asp	Asp	Gly	Gly	Phe	Asn
		355					360					365			
Leu	Arg	Pro	Gly	Val	Glu	Thr	Ser	Ile	Ser	Met	Arg	Lys	Glu	Thr	Leu
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Asp	Arg	Leu	Gly	Gly	Asp	Tyr	Gly	Asp	Cys	Thr	Lys	Asn	Gly	Ser	Asp
385					390					395				400	
Val	Pro	Val	Glu	Asn	Leu	Tyr	Pro	Ser	Lys	Tyr	Thr	Gln	Gln	Val	Cys

Ile	His	Ser	Cys	Phe	Gln	Glu	Ser	Met	Ile	Lys	Glu	Cys	Gly	Cys	Ala
			420					425					430		
Tyr	Ile	Phe	Tyr	Pro	Arg	Pro	Gln	Asn	Val	Glu	Tyr	Cys	Asp	Tyr	Arg
		435					440					445			
Lys	His	Ser	Ser	Trp	Gly	Tyr	Cys	Tyr	Tyr	Lys	Leu	Gln	Val	Asp	Phe
	450					455					460				
Ser	Ser	Asp	His	Leu	Gly	Cys	Phe	Thr	Lys	Cys	Arg	Lys	Pro	Cys	Ser
465					470					475					480
Val	Thr	Ser	Tyr	Gln	Leu	Ser	Ala	Gly	Tyr	Ser	Arg	Trp	Pro	Ser	Val
				485					490					495	
Thr	Ser	Gln	Glu	Trp	Val	Phe	Gln	Met	Leu	Ser	Arg	Gln	Asn	Asn	Tyr
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Thr	Val	Asn	Asn	Lys	Arg	Asn	Gly	Val	Ala	Lys	Val	Asn	Ile	Phe	Phe
		515					520					525			
Lys	Glu	Leu	Asn	Tyr	Lys	Thr	Asn	Ser	Glu	Ser	Pro	Ser	Val	Thr	Met
	530					535					540				
Val	Thr	Leu	Leu	Ser	Asn	Leu	Gly	Ser	Gln	Trp	Ser	Leu	Trp	Phe	Gly
545					550					555					560
Ser	Ser	Val	Leu	Ser	Val	Val	Glu	Met	Ala	Glu	Leu	Val	Phe	Asp	Leu
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Leu	Val	Ile	Met	Phe	Leu	Met	Leu	Leu	Arg	Arg	Phe	Arg	Ser	Arg	Tyr
			580					585					590		
Trp	Ser	Pro	Gly	Arg	Gly	Gly	Arg	Gly	Ala	Gln	Glu	Val	Ala	Ser	Thr
		595					600					605			
Leu	Ala	Ser	Ser	Pro	Pro	Ser	His	Phe	Cys	Pro	His	Pro	Met	Ser	Leu
	610					615					620				
Ser	Leu	Ser	Gln	Pro	Gly	Pro	Ala	Pro	Ser	Pro	Ala	Leu	Thr	Ala	Fro
625					630					635					640
Pro	Pro	Ala	Tyr	Ala	Thr	Leu	Gly	Pro	Arg	Pro	Ser	Pro	Gly	Gly	Ser
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<210> 281
<211> 2892
<212> DNA
<213> Homo sapiens
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<210> 282

<211> 176

<212> PRT

<213> Homo sapiens

<400> 282

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20      25      30
Arg Thr Tyr Ser Gly Ala Phe Val Cys Leu Glu Ile Leu Phe Gly Gly
35      40      45
Leu Val Trp Ile Leu Val Ala Ser Ser Asn Val Pro Leu Pro Leu Leu
50      55      60
Gln Gly Trp Val Met Phe Val Ser Val Thr Ala Phe Phe Phe Ser Leu
65      70      75      80
Leu Phe Leu Gly Met Phe Leu Ser Gly Met Val Ala Gln Ile Asp Ala
85      90      95
Asn Trp Asn Phe Leu Asp Phe Ala Tyr His Phe Thr Val Phe Val Phe
100     105     110
Tyr Phe Gly Ala Phe Leu Leu Glu Ala Ala Ala Thr Ser Leu His Asp
115     120     125
Leu His Cys Asn Thr Thr Ile Thr Gly Gln Pro Leu Leu Ser Asp Asn
130     135     140
Gln Tyr Asn Ile Asn Val Ala Ala Ser Ile Phe Ala Phe Met Thr Thr

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Ala Cys Tyr Gly Cys Ser Leu Gly Leu Ala Leu Arg Arg Trp Arg Pro			
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<210> 283
 <211> 2530
 <212> DNA
 <213> Homo sapiens

<400> 283

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<210> 284
 <211> 771
 <212> PRT

<213> Homo sapiens

<400> 284

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          20           25           30
Lys Leu Ser Tyr Lys Glu Met Leu Glu Ser Asn Asn Val Ile Thr Phe
          35           40           45
Asn Gly Leu Ala Asn Ser Ser Ser Tyr His Thr Phe Leu Leu Asp Glu
          50           55           60
Glu Arg Ser Arg Leu Tyr Val Gly Ala Lys Asp His Ile Phe Ser Phe
65           70           75           80
Asp Leu Val Asn Ile Lys Asp Phe Gln Lys Ile Val Trp Pro Val Ser
          85           90           95
Tyr Thr Arg Arg Asp Glu Cys Lys Trp Ala Gly Lys Asp Ile Leu Lys
          100          105          110
Glu Cys Ala Asn Phe Ile Lys Val Leu Lys Ala Tyr Asn Gln Thr His
          115          120          125
Leu Tyr Ala Cys Gly Thr Gly Ala Phe His Pro Ile Cys Thr Tyr Ile
130          135          140
Glu Ile Gly His His Pro Glu Asp Asn Ile Phe Lys Leu Glu Asn Ser
145          150          155          160
His Phe Glu Asn Gly Arg Gly Lys Ser Pro Tyr Asp Pro Lys Leu Leu
          165          170          175
Thr Ala Ser Leu Leu Ile Asp Gly Glu Leu Tyr Ser Gly Thr Ala Ala
          180          185          190
Asp Phe Met Gly Arg Asp Phe Ala Ile Phe Arg Thr Leu Gly His His
          195          200          205
His Pro Ile Arg Thr Glu Gln His Asp Ser Arg Trp Leu Asn Asp Pro
210          215          220
Lys Phe Ile Ser Ala His Leu Ile Ser Glu Ser Asp Asn Pro Glu Asp
225          230          235          240
Asp Lys Val Tyr Phe Phe Phe Arg Glu Asn Ala Ile Asp Gly Glu His
          245          250          255
Ser Gly Lys Ala Thr His Ala Arg Ile Gly Gln Ile Cys Lys Asn Asp
          260          265          270
Phe Gly Gly His Arg Ser Leu Val Asn Lys Trp Thr Thr Phe Leu Lys
          275          280          285
Ala Arg Leu Ile Cys Ser Val Pro Gly Pro Asn Gly Ile Asp Thr His
290          295          300
Phe Asp Glu Leu Gln Asp Val Phe Leu Met Asn Phe Lys Asp Pro Lys
305          310          315          320
Asn Pro Val Val Tyr Gly Val Phe Thr Thr Ser Ser Asn Ile Phe Lys
          325          330          335
Gly Ser Ala Val Cys Met Tyr Ser Met Ser Asp Val Arg Arg Val Phe
          340          345          350
Leu Gly Pro Tyr Ala His Arg Asp Gly Pro Asn Tyr Gln Trp Val Pro
          355          360          365
Tyr Gln Gly Arg Val Pro Tyr Pro Arg Pro Gly Thr Cys Pro Ser Lys
370          375          380
Thr Phe Gly Gly Phe Asp Ser Thr Lys Asp Leu Pro Asp Asp Val Ile
385          390          395          400
Thr Phe Ala Arg Ser His Pro Ala Met Tyr Asn Pro Val Phe Pro Met
          405          410          415
Asn Asn Arg Pro Ile Val Ile Lys Thr Asp Val Asn Tyr Gln Phe Thr
          420          425          430
Gln Ile Val Val Asp Arg Val Asp Ala Glu Asp Gly Gln Tyr Asp Val

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Thr Val Phe Arg Glu Pro Thr	Ala Ile Ser Ala Met Glu Leu Ser Thr	
485	490	495
Lys Gln Gln Gln Leu Tyr Ile	Gly Ser Thr Ala Gly Val Ala Gln Leu	
500	505	510
Pro Leu His Arg Cys Asp Ile	Tyr Gly Lys Ala Cys Ala Glu Cys Cys	
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Leu Ala Arg Asp Pro Tyr Cys	Ala Trp Asp Gly Ser Ala Cys Ser Arg	
530	535	540
Tyr Phe Pro Thr Ala Lys Arg	Arg Thr Arg Arg Gln Asp Ile Arg Asn	
545	550	555
Gly Asp Pro Leu Thr His Cys	Ser Asp Leu His His Asp Asn His His	
565	570	575
Gly His Ser Pro Glu Glu Arg	Ile Ile Tyr Gly Val Glu Asn Ser Ser	
580	585	590
Thr Phe Leu Glu Cys Ser Pro	Lys Ser Gln Arg Ala Leu Val Tyr Trp	
595	600	605
Gln Phe Gln Arg Arg Asn Glu	Glu Arg Lys Glu Glu Ile Arg Val Asp	
610	615	620
Asp His Ile Ile Arg Thr Asp	Gln Gly Leu Leu Leu Arg Ser Leu Gln	
625	630	635
Gln Lys Asp Ser Gly Asn Tyr	Leu Cys His Ala Val Glu His Gly Phe	
645	650	655
Ile Gln Thr Leu Leu Lys Val	Thr Leu Glu Val Ile Asp Thr Glu His	
660	665	670
Leu Glu Glu Leu Leu His Lys	Asp Asp Asp Gly Asp Gly Ser Lys Thr	
675	680	685
Lys Glu Met Ser Asn Ser Met	Thr Pro Ser Gln Lys Val Trp Tyr Arg	
690	695	700
Asp Phe Met Gln Leu Ile Asn	His Pro Asn Leu Asn Thr Met Asp Glu	
705	710	715
Phe Cys Glu Gln Val Trp Lys	Arg Asp Arg Lys Gln Arg Arg Gln Arg	
725	730	735
Pro Gly His Thr Pro Gly Asn	Ser Asn Lys Trp Lys His Leu Gln Glu	
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Asn Lys Lys Gly Arg Asn Arg	Arg Thr His Glu Phe Glu Arg Ala Pro	
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Arg Ser Val		
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<210> 285

<211> 3041

<212> DNA

<213> Homo sapiens

<400> 285

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<210> 286

<211> 418

<212> PRT

<213> Homo sapiens

<400> 286

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Gln Lys Thr Asp Thr Ser His His Asp Gln Asp His Pro Thr Phe Asn
             35             40             45
Lys Ile Thr Pro Asn Leu Ala Glu Phe Ala Phe Ser Leu Tyr Arg Gln

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294

50	55	60
Leu Ala His Gln Ser Asn Ser Thr Asn Ile Phe Phe Ser Pro Val Ser		
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Ile Ala Thr Ala Phe Ala Met Leu Ser Leu Gly Thr Lys Ala Asp Thr		80
	85	90
His Asp Glu Ile Leu Glu Gly Leu Asn Phe Asn Leu Thr Glu Ile Pro		95
	100	105
Glu Ala Gln Ile His Glu Gly Phe Gln Glu Leu Leu Arg Thr Leu Asn		110
	115	120
Gln Pro Asp Ser Gln Leu Gln Leu Thr Thr Gly Asn Gly Leu Phe Leu		125
	130	135
Ser Glu Gly Leu Lys Leu Val Asp Lys Phe Leu Glu Asp Val Lys Lys		140
145	150	155
Leu Tyr His Ser Glu Ala Phe Thr Val Asn Phe Gly Asp Thr Glu Glu		160
	165	170
Ala Lys Lys Gln Ile Asn Asp Tyr Val Glu Lys Gly Thr Gln Gly Lys		175
	180	185
Ile Val Asp Leu Val Lys Glu Leu Asp Arg Asp Thr Val Phe Ala Leu		190
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Val Asn Tyr Ile Phe Phe Lys Gly Lys Trp Glu Arg Pro Phe Glu Val		205
	210	215
Lys Asp Thr Glu Glu Glu Asp Phe His Val Asp Gln Val Thr Thr Val		220
225	230	235
Lys Val Pro Met Met Lys Arg Leu Gly Met Phe Asn Ile Gln His Cys		240
	245	250
Lys Lys Leu Ser Ser Trp Val Leu Leu Met Lys Tyr Leu Gly Asn Ala		255
	260	265
Thr Ala Ile Phe Phe Leu Pro Asp Glu Gly Lys Leu Gln His Leu Glu		270
	275	280
Asn Glu Leu Thr His Asp Ile Ile Thr Lys Phe Leu Glu Asn Glu Asp		285
	290	295
Arg Arg Ser Ala Ser Leu His Leu Pro Lys Leu Ser Ile Thr Gly Thr		300
305	310	315
Tyr Asp Leu Lys Ser Val Leu Gly Gln Leu Gly Ile Thr Lys Val Phe		320
	325	330
Ser Asn Gly Ala Asp Leu Ser Gly Val Thr Glu Glu Ala Pro Leu Lys		335
	340	345
Leu Ser Lys Ala Val His Lys Ala Val Leu Thr Ile Asp Glu Lys Gly		350
	355	360
Thr Glu Ala Ala Gly Ala Met Phe Leu Glu Ala Ile Pro Met Ser Ile		365
	370	375
Pro Pro Glu Val Lys Phe Asn Lys Pro Phe Val Phe Leu Met Ile Glu		380
385	390	395
Gln Asn Thr Lys Ser Pro Leu Phe Met Gly Lys Val Val Asn Pro Thr		400
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Gln Lys

<210> 287

<211> 3928

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(3928)

<223> n = A,T,C or G

<400> 287

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<210> 288

<211> 293

<212> PRT

<213> Homo sapiens

<400> 288

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Trp Asn Trp Ile Trp Arg Arg Cys Cys Arg Ala Ala Ser Ala Ala Val
  35          40          45
Leu Ala Pro Leu Gly Phe Thr Leu Arg Lys Pro Pro Ala Val Gly Arg
  50          55          60
Asn Arg Arg His His Arg His Pro Arg Gly Gly Ser Cys Leu Ala Ala
  65          70          75          80
Ala His His Arg Met Arg Trp Arg Ala Asp Gly Arg Ser Leu Glu Lys
  85          90          95
Leu Pro Val His Met Gly Leu Val Ile Thr Glu Val Glu Gln Glu Pro
  100         105         110
Ser Phe Ser Asp Ile Ala Ser Leu Val Val Trp Cys Met Ala Val Gly
  115         120         125
Ile Ser Tyr Ile Ser Val Tyr Asp His Gln Gly Ile Phe Lys Arg Asn
  130         135         140
Asn Ser Arg Leu Met Asp Glu Ile Leu Lys Gln Gln Gln Glu Leu Leu
  145         150         155         160
Gly Leu Asp Cys Ser Lys Tyr Ser Pro Glu Phe Ala Asn Ser Asn Asp
  165         170         175
Lys Asp Asp Gln Val Leu Asn Cys His Leu Ala Val Lys Val Leu Ser
  180         185         190
Pro Glu Asp Gly Lys Ala Asp Ile Val Arg Ala Ala Gln Asp Phe Cys
  195         200         205
Gln Leu Val Ala Gln Lys Gln Lys Arg Pro Thr Asp Leu Asp Val Asp
  210         215         220
Thr Leu Ala Ser Leu Leu Ser Ser Asn Gly Cys Pro Asp Pro Asp Leu
  225         230         235         240
Val Leu Lys Phe Gly Pro Val Asp Ser Thr Leu Gly Phe Leu Pro Trp
  245         250         255
His Ile Arg Leu Thr Glu Ile Val Ser Leu Pro Ser His Leu Asn Ile
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Gln Arg Leu Gly Lys
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<210> 289

<211> 936
 <212> DNA
 <213> Homo sapiens

<400> 289

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<210> 290
 <211> 248
 <212> PRT
 <213> Homo sapiens

<400> 290

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Met Ser Ser Ile Gly Thr Gly Tyr Asp Leu Ser Ala Ser Thr Phe Ser
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          20          25          30
Asn Ser Ser Thr Ala Ile Gly Ile Arg Cys Lys Asp Gly Val Val Phe
          35          40          45
Gly Val Glu Lys Leu Val Leu Ser Lys Leu Tyr Glu Glu Gly Ser Asn
          50          55          60
Lys Arg Leu Phe Asn Val Asp Arg His Val Gly Met Ala Val Ala Gly
65          70          75          80
Leu Leu Ala Asp Ala Arg Ser Leu Ala Asp Ile Ala Arg Glu Glu Ala
          85          90          95
Ser Asn Phe Arg Ser Asn Phe Gly Tyr Asn Ile Pro Leu Lys His Leu
          100         105         110
Ala Asp Arg Val Ala Met Tyr Val His Ala Tyr Thr Leu Tyr Ser Ala
          115         120         125
Val Arg Pro Phe Gly Cys Ser Val Asn Asp Gly Ala Gln Leu Tyr Met
          130         135         140
Ile Asp Pro Ser Gly Val Ser Tyr Gly Tyr Trp Gly Cys Ala Ile Gly
145         150         155         160
Lys Ala Arg Gln Ala Ala Lys Thr Glu Ile Glu Lys Leu Gln Met Lys
          165         170         175
Glu Met Thr Cys Arg Asp Ile Val Lys Glu Val Ala Lys Ile Ile Tyr
          180         185         190
Ile Val His Asp Glu Val Lys Asp Lys Ala Phe Glu Leu Glu Leu Ser
          195         200         205
Trp Val Gly Glu Leu Thr Asn Gly Arg His Glu Ile Val Pro Lys Asp
          210         215         220
Ile Arg Glu Glu Ala Glu Lys Tyr Ala Lys Glu Ser Leu Lys Glu Glu
225         230         235         240
  
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Asp Glu Ser Asp Asp Asp Asn Met
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<210> 291
<211> 2782
<212> DNA
<213> Homo sapiens

<400> 291

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<210> 292
 <211> 461
 <212> PRT
 <213> Homo sapiens

<400> 292

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		35				40					45				
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His	Ile	Pro	Glu	Arg	Leu	Cys	Glu	Ser	Lys	Glu	Gly	Gly	Gln	Gly	Glu
65					70				75						80
Glu	Thr	Phe	Ser	Gln	Ile	Pro	Asp	Gly	Ile	Leu	Asn	Lys	Lys	Thr	Pro
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Pro	Ser	Ser	Leu	Asn	Arg	His	Ile	Arg	Asp	His	Thr	Gly	Arg	Glu	Pro
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His	Pro	Gly	Gly	Lys	Pro	Tyr	Asp	Cys	Lys	Glu	Cys	Gly	Glu	Thr	Phe
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Ile	Ser	Leu	Val	Ser	Ile	Arg	Arg	His	Met	Leu	Thr	His	Arg	Gly	Gly
		180						185					190		
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Lys	Leu	Phe	Glu	Cys	Lys	Glu	Cys	Gly	Lys	Ala	Leu	Thr	Cys	Leu	Ala
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Ser	Val	Arg	Arg	His	Met	Ile	Lys	His	Thr	Gly	Asn	Gly	Pro	Tyr	Lys
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Cys	Lys	Val	Cys	Gly	Lys	Ala	Phe	Asp	Phe	Pro	Ser	Ser	Phe	Arg	Ile
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His	Glu	Arg	Thr	His	Thr	Gly	Glu	Lys	Pro	Tyr	Asp	Cys	Lys	Gln	Cys
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Gly	Lys	Ala	Phe	Ser	Cys	Ser	Ser	Ser	Phe	Arg	Lys	His	Glu	Arg	Ile
	370					375					380				
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300

Lys Pro Tyr Glu Cys Lys Gln Cys Gly Lys Ala Phe Ser Arg Ser Thr
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 <212> DNA
 <213> Homo sapiens

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301

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 Pro Glu Cys Gln Ser Asp Trp Gln Cys Pro Gly Lys Lys Arg Cys Cys
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Lys	Glu	Asp	Leu	Arg	Pro	Ser	Ala	Pro	Gln	Gln	Glu	Gly	Val	Ala	Ser
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<400> 299

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<210> 300

<211> 2214

<212> PRT

<213> Homo sapiens

<400> 300

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Lys	Tyr	Met	Phe	Ala	Thr	Lys	Val	Val	His	Leu	Leu	Gly	Ser	Glu	Gln		
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Gln	Ser	Ser	Val	Gln	Leu	Trp	Val	Ser	Phe	Gly	Arg	Lys	Pro	Met	Arg		
				325					330					335			
Ala	Ala	Gln	Phe	Val	Thr	Arg	His	Pro	Ile	Asn	Glu	Tyr	Tyr	Ile	Ala		
			340					345					350				
Asp	Ala	Ser	Glu	Asp	Gln	Val	Phe	Val	Cys	Val	Ser	His	Ser	Asn	Asn		
		355					360					365					
Arg	Thr	Asn	Leu	Tyr	Ile	Ser	Glu	Ala	Glu	Gly	Leu	Lys	Phe	Ser	Leu		
	370					375					380						
Ser	Leu	Glu	Asn	Val	Leu	Tyr	Tyr	Ser	Pro	Gly	Gly	Ala	Gly	Ser	Asp		
385					390					395					400		
Thr	Leu	Val	Arg	Tyr	Phe	Ala	Asn	Glu	Pro	Phe	Ala	Asp	Phe	His	Arg		
			405					410						415			
Val	Glu	Gly	Leu	Gln	Gly	Val	Tyr	Ile	Ala	Thr	Leu	Ile	Asn	Gly	Ser		
			420					425					430				
Met	Asn	Glu	Glu	Asn	Met	Arg	Ser	Val	Ile	Thr	Phe	Asp	Lys	Gly	Gly		
		435					440					445					
Thr	Trp	Glu	Phe	Leu	Gln	Ala	Pro	Ala	Phe	Thr	Gly	Tyr	Gly	Glu	Lys		
	450				455						460						
Ile	Asn	Cys	Glu	Leu	Ser	Gln	Gly	Cys	Ser	Leu	His	Leu	Ala	Gln	Arg		
465					470					475					480		
Leu	Ser	Gln	Leu	Leu	Asn	Leu	Gln	Leu	Arg	Arg	Met	Pro	Ile	Leu	Ser		
			485					490						495			
Lys	Glu	Ser	Ala	Pro	Gly	Leu	Ile	Ile	Ala	Thr	Gly	Ser	Val	Gly	Lys		
			500					505					510				
Asn	Leu	Ala	Ser	Lys	Thr	Asn	Val	Tyr	Ile	Ser	Ser	Ser	Ala	Gly	Ala		
		515					520					525					
Arg	Trp	Arg	Glu	Ala	Leu	Pro	Gly	Pro	His	Tyr	Tyr	Thr	Trp	Gly	Asp		
	530					535					540						
His	Gly	Gly	Ile	Ile	Thr	Ala	Ile	Ala	Gln	Gly	Met	Glu	Thr	Asn	Glu		
545					550					555					560		
Leu	Lys	Tyr	Ser	Thr	Asn	Glu	Gly	Glu	Thr	Trp	Lys	Thr	Phe	Ile	Phe		
			565					570						575			
Ser	Glu	Lys	Pro	Val	Phe	Val	Tyr	Gly	Leu	Leu	Thr	Glu	Pro	Gly	Glu		
			580					585					590				
Lys	Ser	Thr	Val	Phe	Thr	Ile	Phe	Gly	Ser	Asn	Lys	Glu	Asn	Val	His		
		595					600					605					
Ser	Trp	Leu	Ile	Leu	Gln	Val	Asn	Ala	Thr	Asp	Ala	Leu	Gly	Val	Pro		
	610					615					620						
Cys	Thr	Glu	Asn	Asp	Tyr	Lys	Leu	Trp	Ser	Pro	Ser	Asp	Glu	Arg	Gly		
625					630					635					640		
Asn	Glu	Cys	Leu	Leu	Gly	His	Lys	Thr	Val	Phe	Lys	Arg	Arg	Thr	Pro		
			645					650						655			
His	Ala	Thr	Cys	Phe	Asn	Gly	Glu	Asp	Phe	Asp	Arg	Pro	Val	Val	Val		
			660					665					670				
Ser	Asn	Cys	Ser	Cys	Thr	Arg	Glu	Asp	Tyr	Glu	Cys	Asp	Phe	Gly	Phe		
		675					680					685					
Lys	Met	Ser	Glu	Asp	Leu	Ser	Leu	Glu	Val	Cys	Val	Pro	Asp	Pro	Glu		
	690					695					700						

Phe	Ser	Gly	Lys	Ser	Tyr	Ser	Pro	Pro	Val	Pro	Cys	Pro	Val	Gly	Ser	705	710	715	720
Thr	Tyr	Arg	Arg	Thr	Arg	Gly	Tyr	Arg	Lys	Ile	Ser	Gly	Asp	Thr	Cys	725	730	735	
Ser	Gly	Gly	Asp	Val	Glu	Ala	Arg	Leu	Glu	Gly	Glu	Leu	Val	Pro	Cys	740	745	750	
Pro	Leu	Ala	Glu	Glu	Asn	Glu	Phe	Ile	Leu	Tyr	Ala	Val	Arg	Lys	Ser	755	760	765	
Ile	Tyr	Arg	Tyr	Asp	Leu	Ala	Ser	Gly	Ala	Thr	Glu	Gln	Leu	Pro	Leu	770	775	780	
Thr	Gly	Leu	Arg	Ala	Ala	Val	Ala	Leu	Asp	Phe	Asp	Tyr	Glu	His	Asn	785	790	795	800
Cys	Leu	Tyr	Trp	Ser	Asp	Leu	Ala	Leu	Asp	Val	Ile	Gln	Arg	Leu	Cys	805	810	815	
Leu	Asn	Gly	Ser	Thr	Gly	Gln	Glu	Val	Ile	Ile	Asn	Ser	Gly	Leu	Glu	820	825	830	
Thr	Val	Glu	Ala	Leu	Ala	Phe	Glu	Pro	Leu	Ser	Gln	Leu	Leu	Tyr	Trp	835	840	845	
Val	Asp	Ala	Gly	Phe	Lys	Lys	Ile	Glu	Val	Ala	Asn	Pro	Asp	Gly	Asp	850	855	860	
Phe	Arg	Leu	Thr	Ile	Val	Asn	Ser	Ser	Val	Leu	Asp	Arg	Pro	Arg	Ala	865	870	875	880
Leu	Val	Leu	Val	Pro	Gln	Glu	Gly	Val	Met	Phe	Trp	Thr	Asp	Trp	Gly	885	890	895	
Asp	Leu	Lys	Pro	Gly	Ile	Tyr	Arg	Ser	Asn	Met	Asp	Gly	Ser	Ala	Ala	900	905	910	
Tyr	His	Leu	Val	Ser	Glu	Asp	Val	Lys	Trp	Pro	Asn	Gly	Ile	Ser	Val	915	920	925	
Asp	Asp	Gln	Trp	Ile	Tyr	Trp	Thr	Asp	Ala	Tyr	Leu	Glu	Cys	Ile	Glu	930	935	940	
Arg	Ile	Thr	Phe	Ser	Gly	Gln	Gln	Arg	Ser	Val	Ile	Leu	Asp	Asn	Leu	945	950	955	960
Pro	His	Pro	Tyr	Ala	Ile	Ala	Val	Phe	Lys	Asn	Glu	Ile	Tyr	Trp	Asp	965	970	975	
Asp	Trp	Ser	Gln	Leu	Ser	Ile	Phe	Arg	Ala	Ser	Lys	Tyr	Ser	Gly	Ser	980	985	990	
Gln	Met	Glu	Ile	Leu	Ala	Asn	Gln	Leu	Thr	Gly	Leu	Met	Asp	Met	Lys	995	1000	1005	
Ile	Phe	Tyr	Lys	Gly	Lys	Asn	Thr	Gly	Ser	Asn	Ala	Cys	Val	Pro	Arg	1010	1015	1020	
Pro	Cys	Ser	Leu	Leu	Cys	Leu	Pro	Lys	Ala	Asn	Asn	Ser	Arg	Ser	Cys	1025	1030	1035	1040
Arg	Cys	Pro	Glu	Asp	Val	Ser	Ser	Ser	Val	Leu	Pro	Ser	Gly	Asp	Leu	1045	1050	1055	
Met	Cys	Asp	Cys	Pro	Gln	Gly	Tyr	Gln	Leu	Lys	Asn	Asn	Thr	Cys	Val	1060	1065	1070	
Lys	Glu	Glu	Asn	Thr	Cys	Leu	Arg	Asn	Gln	Tyr	Arg	Cys	Ser	Asn	Gly	1075	1080	1085	
Asn	Cys	Ile	Asn	Ser	Ile	Trp	Trp	Cys	Asp	Phe	Asp	Asn	Asp	Cys	Gly	1090	1095	1100	
Asp	Met	Ser	Asp	Glu	Arg	Asn	Cys	Pro	Thr	Thr	Ile	Cys	Asp	Leu	Asp	1105	1110	1115	1120
Thr	Gln	Phe	Arg	Cys	Gln	Glu	Ser	Gly	Thr	Cys	Ile	Pro	Leu	Ser	Tyr	1125	1130	1135	
Lys	Cys	Asp	Leu	Glu	Asp	Asp	Cys	Gly	Asp	Asn	Ser	Asp	Glu	Ser	His	1140	1145	1150	
Cys	Glu	Met	His	Gln	Cys	Arg	Ser	Asp	Glu	Tyr	Asn	Cys	Ser	Ser	Gly	1155	1160	1165	

Met Cys Ile Arg Ser Ser Trp Val Cys Asp Gly Asp Asn Asp Cys Arg
 1170 1175 1180
 Asp Trp Ser Asp Glu Ala Asn Cys Thr Ala Ile Tyr His Thr Cys Glu
 1185 1190 1195 1200
 Ala Ser Asn Phe Gln Cys Arg Asn Gly His Cys Ile Pro Gln Arg Trp
 1205 1210 1215
 Ala Cys Asp Gly Asp Thr Asp Cys Gln Asp Gly Ser Asp Glu Asp Pro
 1220 1225 1230
 Val Asn Cys Glu Lys Lys Cys Asn Gly Phe Arg Cys Pro Asn Gly Thr
 1235 1240 1245
 Cys Ile Pro Ser Ser Lys His Cys Asp Gly Leu Arg Asp Cys Ser Asp
 1250 1255 1260
 Gly Ser Asp Glu Gln His Cys Glu Pro Leu Cys Thr His Phe Met Asp
 1265 1270 1275 1280
 Phe Val Cys Lys Asn Arg Gln Gln Cys Leu Phe His Ser Met Val Cys
 1285 1290 1295
 Asp Gly Ile Ile Gln Cys Arg Asp Gly Ser Asp Glu Asp Ala Ala Phe
 1300 1305 1310
 Ala Gly Cys Ser Gln Asp Pro Glu Phe His Lys Val Cys Asp Glu Phe
 1315 1320 1325
 Gly Phe Gln Cys Gln Asn Gly Val Cys Ile Ser Leu Ile Trp Lys Cys
 1330 1335 1340
 Asp Gly Met Asp Asp Cys Gly Asp Tyr Ser Asp Glu Ala Asn Cys Glu
 1345 1350 1355 1360
 Asn Pro Thr Glu Ala Pro Asn Cys Ser Arg Tyr Phe Gln Phe Arg Cys
 1365 1370 1375
 Glu Asn Gly His Cys Ile Pro Asn Arg Trp Lys Cys Asp Arg Glu Asn
 1380 1385 1390
 Asp Cys Gly Asp Trp Ser Asp Glu Lys Asp Cys Gly Asp Ser His Ile
 1395 1400 1405
 Leu Pro Phe Ser Thr Pro Gly Pro Ser Thr Cys Leu Pro Asn Tyr Tyr
 1410 1415 1420
 Arg Cys Ser Ser Gly Thr Cys Val Met Asp Thr Trp Val Cys Asp Gly
 1425 1430 1435 1440
 Tyr Arg Asp Cys Ala Asp Gly Ser Asp Glu Glu Ala Cys Pro Leu Leu
 1445 1450 1455
 Ala Asn Val Thr Ala Ala Ser Thr Pro Thr Gln Leu Gly Arg Cys Asp
 1460 1465 1470
 Arg Phe Glu Phe Glu Cys His Gln Pro Lys Thr Cys Ile Pro Asn Trp
 1475 1480 1485
 Lys Arg Cys Asp Gly His Gln Asp Cys Gln Asp Gly Arg Asp Glu Ala
 1490 1495 1500
 Asn Cys Pro Thr His Ser Thr Leu Thr Cys Met Ser Arg Glu Phe Gln
 1505 1510 1515 1520
 Cys Glu Asp Gly Glu Ala Cys Ile Val Leu Ser Glu Arg Cys Asp Gly
 1525 1530 1535
 Phe Leu Asp Cys Ser Asp Glu Ser Asp Glu Lys Ala Cys Ser Asp Glu
 1540 1545 1550
 Leu Thr Val Tyr Lys Val Gln Asn Leu Gln Trp Thr Ala Asp Phe Ser
 1555 1560 1565
 Gly Asp Val Thr Leu Thr Trp Met Arg Pro Lys Lys Met Pro Ser Ala
 1570 1575 1580
 Ser Cys Val Tyr Asn Val Tyr Tyr Arg Val Val Gly Glu Ser Ile Trp
 1585 1590 1595 1600
 Lys Thr Leu Glu Thr His Ser Asn Lys Thr Asn Thr Val Leu Lys Val
 1605 1610 1615
 Leu Lys Pro Asp Thr Thr Tyr Gln Val Lys Val Gln Val Gln Cys Leu
 1620 1625 1630

Ser Lys Ala His Asn Thr Asn Asp Phe Val Thr Leu Arg Thr Pro Glu
 1635 1640 1645
 Gly Leu Pro Asp Ala Pro Arg Asn Leu Gln Leu Ser Leu Pro Arg Glu
 1650 1655 1660
 Ala Glu Gly Val Ile Val Gly His Trp Ala Pro Pro Ile His Thr His
 1665 1670 1675 1680
 Gly Leu Ile Arg Glu Tyr Ile Val Glu Tyr Ser Arg Ser Gly Ser Lys
 1685 1690 1695
 Met Trp Ala Ser Gln Arg Ala Ala Ser Asn Phe Thr Glu Ile Lys Asn
 1700 1705 1710
 Leu Leu Val Asn Thr Leu Tyr Thr Val Arg Val Ala Ala Val Thr Ser
 1715 1720 1725
 Arg Gly Ile Gly Asn Trp Ser Asp Ser Lys Ser Ile Thr Thr Ile Lys
 1730 1735 1740
 Gly Lys Val Ile Pro Pro Pro Asp Ile His Ile Asp Ser Tyr Gly Glu
 1745 1750 1755 1760
 Asn Tyr Leu Ser Phe Thr Leu Thr Met Glu Ser Asp Ile Lys Val Asn
 1765 1770 1775
 Gly Tyr Val Val Asn Leu Phe Trp Ala Phe Asp Thr His Lys Gln Glu
 1780 1785 1790
 Arg Arg Thr Leu Asn Phe Arg Gly Ser Ile Leu Ser His Lys Val Gly
 1795 1800 1805
 Asn Leu Thr Ala His Thr Ser Tyr Glu Ile Ser Ala Trp Ala Lys Thr
 1810 1815 1820
 Asp Leu Gly Asp Ser Pro Leu Ala Phe Glu His Val Met Thr Arg Gly
 1825 1830 1835 1840
 Val Arg Pro Pro Ala Pro Ser Leu Lys Ala Lys Ala Ile Asn Gln Thr
 1845 1850 1855
 Ala Val Glu Cys Thr Trp Thr Gly Pro Arg Asn Val Val Tyr Gly Ile
 1860 1865 1870
 Phe Tyr Ala Thr Ser Phe Leu Asp Leu Tyr Arg Asn Pro Lys Ser Leu
 1875 1880 1885
 Thr Thr Ser Leu His Asn Lys Thr Val Ile Val Ser Lys Asp Glu Gln
 1890 1895 1900
 Tyr Leu Phe Leu Val Arg Val Val Val Pro Tyr Gln Gly Pro Ser Ser
 1905 1910 1915 1920
 Asp Tyr Val Val Val Lys Met Ile Pro Asp Ser Arg Leu Pro Pro Arg
 1925 1930 1935
 His Leu His Val Val His Thr Gly Lys Thr Ser Val Val Ile Lys Trp
 1940 1945 1950
 Glu Ser Pro Tyr Asp Ser Pro Asp Gln Asp Leu Leu Tyr Ala Ile Ala
 1955 1960 1965
 Val Lys Asp Leu Ile Arg Lys Thr Asp Arg Ser Tyr Lys Val Lys Ser
 1970 1975 1980
 Arg Asn Ser Thr Val Glu Tyr Thr Leu Asn Lys Leu Glu Pro Gly Gly
 1985 1990 1995 2000
 Lys Tyr His Ile Ile Val Gln Leu Gly Asn Met Ser Lys Asp Ser Ser
 2005 2010 2015
 Ile Lys Ile Thr Thr Val Ser Leu Ser Ala Pro Asp Ala Leu Lys Ile
 2020 2025 2030
 Ile Thr Glu Asn Asp His Val Leu Leu Phe Trp Lys Ser Leu Ala Leu
 2035 2040 2045
 Lys Glu Lys His Phe Asn Glu Ser Arg Gly Tyr Glu Ile His Met Phe
 2050 2055 2060
 Asp Ser Ala Met Asn Ile Thr Ala Tyr Leu Gly Asn Thr Thr Asp Asn
 2065 2070 2075 2080
 Phe Phe Lys Ile Ser Asn Leu Lys Met Gly His Asn Tyr Thr Phe Thr
 2085 2090 2095

309

Val Gln Ala Arg Cys Leu Phe Gly Asn Gln Ile Cys Gly Glu Pro Ala
 2100 2105 2110
 Ile Leu Leu Tyr Asp Glu Leu Gly Ser Gly Ala Asp Ala Ser Ala Thr
 2115 2120 2125
 Gln Ala Ala Arg Ser Thr Asp Val Ala Ala Val Val Val Pro Ile Leu
 2130 2135 2140
 Phe Leu Ile Leu Leu Ser Leu Gly Val Gly Phe Ala Ile Leu Tyr Thr
 2145 2150 2155 2160
 Lys His Arg Arg Leu Gln Ser Ser Phe Thr Ala Phe Ala Asn Ser His
 2165 2170 2175
 Tyr Ser Ser Arg Leu Gly Ser Ala Ile Phe Ser Ser Gly Asp Asp Leu
 2180 2185 2190
 Gly Glu Asp Asp Glu Asp Ala Pro Met Ile Thr Gly Phe Ser Asp Asp
 2195 2200 2205
 Val Pro Met Val Ile Ala
 2210

<210> 301
 <211> 1544
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(1544)
 <223> n = A,T,C or G

<400> 301
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 cggcgagggc gcgagtgagg agcagaccca ggcacgcgc gccgagaagg ccgggcgtcc 120
 ccacactgaa ggtccgga aa ggcgacttcc gggggctttg gcacctggcg gacctccc 180
 gagcgtcggc acctgaacgc gaggcgctcc attgcgcgtg cgcgttgagg ggcttcccgc 240
 acctgatcg gagacccaa cggctggtgg cgtgcctgc gcgtctcggc tgagctggcc 300
 atggcgagc tgtgcgggct gaggcggagc cgggcgtttc tgcacctgct gggatcgctg 360
 ctctctctg gggctctggc ggccgaccga gaacgcagca tccacgactt ctgcctgggtg 420
 tcgaaggtgg tgggcagatg ccgggcctcc atgcctagggt ggtggtacaa tgtcactgac 480
 ggatcctgcc agctgtttgt gtatgggggc tgtgacggaa acagcaataa ttacctgacc 540
 aaggaggagt gcctcaagaa atgtgccact gtcacagaga atgccacggg tgacctggcc 600
 accagcagga atgcagcgga ttcctctgtc ccaagtgtc ccagaaggca ggattctgaa 660
 gacctcca gcgatatgtt caactatgaa gaatactgca ccgccaacgc agtcaactggg 720
 ccttgccgtg catccttccc acgctggtac tttgacgtgg agaggaactc ctgcaataac 780
 ttcatctatg gaggtgccg gggcaataag aacagctacc gctctgagga ggcctgcatg 840
 ctccgtgct tccgccagca ggagaatcct cccctgccc ttggctcaaa ggtggtggtt 900
 ctggcggggc tgttcgtgat ggtgttgatc ctcttctgg gagcctccat ggtctacctg 960
 atccgggtgg cacggaggaa ccaggagcgt gccctgcgca ccgtctggag ctccggagat 1020
 gacaaggagc agctggtgaa gaacacatat gtcctgtgac cgccctgtcg ccaagaggac 1080
 tggggaaggg aggggagact atgtgtgagc tttttttaa tagagggatt gactcggatt 1140
 tgagtgatca ttagggctga ggtctgtttc tctgggagggt aggacggctg cttcctggtc 1200
 tggcagggat gggtttgctt tggaaatcct ctaggaggct cctcctcgca tggcctgcag 1260
 tctggcagca gcccagagt gtttctcgc tgatcgattt ctttctcca ggtagagttt 1320
 tctttgctta tgttgaattc cattgcctcc ttttctcnat cacagaagtg atgttggaat 1380
 cgtttctttt gtttgtctga tttatggttt ttttaagtat aaacaaaagt tttttattag 1440
 cattctgaaa gaaggaaagt aaaatgtaca agtttaataa aaaggggcct tcccctttag 1500
 aataaatttc cagcatgttg ctttcaaaaa aaaaaaaaaa aaaa 1544

<210> 302
 <211> 252

<212> PRT

<213> Homo sapiens

<400> 302

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 20           25           30
Ser Ile His Asp Phe Cys Leu Val Ser Lys Val Val Gly Arg Cys Arg
 35           40           45
Ala Ser Met Pro Arg Trp Trp Tyr Asn Val Thr Asp Gly Ser Cys Gln
 50           55           60
Leu Phe Val Tyr Gly Gly Cys Asp Gly Asn Ser Asn Asn Tyr Leu Thr
 65           70           75           80
Lys Glu Glu Cys Leu Lys Lys Cys Ala Thr Val Thr Glu Asn Ala Thr
 85           90           95
Gly Asp Leu Ala Thr Ser Arg Asn Ala Ala Asp Ser Ser Val Pro Ser
100           105           110
Ala Pro Arg Arg Gln Asp Ser Glu Asp His Ser Ser Asp Met Phe Asn
115           120           125
Tyr Glu Glu Tyr Cys Thr Ala Asn Ala Val Thr Gly Pro Cys Arg Ala
130           135           140
Ser Phe Pro Arg Trp Tyr Phe Asp Val Glu Arg Asn Ser Cys Asn Asn
145           150           155           160
Phe Ile Tyr Gly Gly Cys Arg Gly Asn Lys Asn Ser Tyr Arg Ser Glu
165           170           175
Glu Ala Cys Met Leu Arg Cys Phe Arg Gln Gln Glu Asn Pro Pro Leu
180           185           190
Pro Leu Gly Ser Lys Val Val Val Leu Ala Gly Leu Phe Val Met Val
195           200           205
Leu Ile Leu Phe Leu Gly Ala Ser Met Val Tyr Leu Ile Arg Val Ala
210           215           220
Arg Arg Asn Gln Glu Arg Ala Leu Arg Thr Val Trp Ser Ser Gly Asp
225           230           235           240
Asp Lys Glu Gln Leu Val Lys Asn Thr Tyr Val Leu
245           250

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<210> 303

<211> 1558

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(1558)

<223> n = A,T,C or G

<400> 303

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gaacgcgctg agggccggtg agtgctgcag gcggcgaggg cgcgagttag gacgagaccc 120
aggcatcgcg cgccgagaag gccgggcgtc cccacactga aggtccggaaggcgcacttc 180
cgggggcttt ggcacctggc ggacctccc ggagcgtcgg cacctgaacg cgaggcgctc 240
cattgcgcgt gcgcgttgag gggcttccc cactgatcg cgagaccca acggctgggtg 300
gcgtgcgctg cgcgctcctg ctgagctggc catggcgag ctgtgcgggc tgaggcgagg 360
ccgggcgttt ctgcacctgc tgggatcgct gtcctctct ggggtcctgg cggccgaccg 420
agaacgcagc atccacgaga atgccacggg tgacctggcc accagcagga atgcagcgga 480
ttcctctgtc ccaagtgtc ccagaaggca ggattctgaa gaccactcca gcgatatgtt 540

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caactatgaa gaatactgca cgcgcaacgc agtcaactggg ccttgccgtg catccttccc 600
acgctggtac tttgacgtgg agaggaactc ctgcaataac ttcatctatg gaggctgccg 660
gggcaataag aacagctacc gctctgagga ggcctgcatg ctccgctgct tccgccagca 720
ggagaatcct cccctgcccc ttggtctaaa ggtggtgstt ctggcggggc tgttcgtgat 780
ggtgttgatc ctcttctctg gagcctccat ggtctacctg atccgggtgg cacggaggaa 840
ccaggagcgt gccctgcgca ccgtctggag ctccggagat gacaaggagc agctggtgaa 900
gaacacatat gtctgtgac cgccctgtcg ccaagaggac tggggaaggg aggggagact 960
atgtgtgagc tttttttaa tagagggatt gactcggatt tgagtgatca ttagggctga 1020
ggtctgtttc tctgggaggt aggacggctg ctctctggtc tggcagggat gggtttgctt 1080
tggaatcct ctaggaggct cctcctcgca tggcctgcag tctggcagca gccccgagtt 1140
gtttcctcgc tgatcgattt ctttctcca ggtagagttt tctttgctta tgttgattc 1200
cattgcctct tttctcatca cagaagtgat gttggaatcg tttcttttgt ttgtctgatt 1260
tatggttttt ttaagtataa acaaaagttt tttattagca ttctgaaaga aggaaagtaa 1320
aatgtacctn cgcccgnnnc gancrcctcg amcbttccch htaraawaaa wwwmarmawr 1380
tgctttcttt atgggagtc taatttcaac cctaccaaaa tgatcacaag aactatctg 1440
aggtgtccca ttctagaaat agaccctca aaatagcgtc tttcagatct ttttgatga 1500
atccacaaga tgaaataaat gtcctattac tgaaaaaaa aaaaaaaagg gcggccgc 1558

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<210> 304

<211> 195

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(195)

<223> Xaa = Any Amino Acid

<400> 304

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 20          25          30
Ser Ile His Glu Asn Ala Thr Gly Asp Leu Ala Thr Ser Arg Asn Ala
 35          40          45
Ala Asp Ser Ser Val Pro Ser Ala Pro Arg Arg Gln Asp Ser Glu Asp
 50          55          60
His Ser Ser Asp Met Phe Asn Tyr Glu Glu Tyr Cys Thr Ala Asn Ala
 65          70          75          80
Val Thr Gly Pro Cys Arg Ala Ser Phe Pro Arg Trp Tyr Phe Asp Val
 85          90          95
Glu Arg Asn Ser Cys Asn Asn Phe Ile Tyr Gly Gly Cys Arg Gly Asn
100         105         110
Lys Asn Ser Tyr Arg Ser Glu Glu Ala Cys Met Leu Arg Cys Phe Arg
115         120         125
Gln Gln Glu Asn Pro Pro Leu Pro Leu Gly Ser Lys Val Val Xaa Leu
130         135         140
Ala Gly Leu Phe Val Met Val Leu Ile Leu Phe Leu Gly Ala Ser Met
145         150         155         160
Val Tyr Leu Ile Arg Val Ala Arg Arg Asn Gln Glu Arg Ala Leu Arg
165         170         175
Thr Val Trp Ser Ser Gly Asp Asp Lys Glu Gln Leu Val Lys Asn Thr
180         185         190
Tyr Val Leu
195

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<210> 305

<211> 3079
 <212> DNA
 <213> Homo sapiens

<400> 305

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actccggcac tgctggccct ggcgctgccc ctggccgcgg cgctggcctt ctccgacgag 120
accctggaca aagtgcccaa gtcagagggc tactgtagcc gtatcctgcg cgcccagggc 180
acgcgggcgc agggctacac cgagttcagc ctccgcgtgg agggcgaccc cgacttctac 240
aagccgggaa ccagctaccg cgtaacactt tcagctgctc ctccctccta cttcagagga 300
ttcacattaa ttgccctcag agagaacaga gagggtgata aggaagaaga ccatgctggg 360
accttcaga tcatagacga agaagaaact cagtttatga gcaattgccc tgttgagtc 420
actgaaagca ctccacggag gaggaccgg atccagggtg tttggatagc accaccagcg 480
ggaacaggct gcgtgattct gaaggccagc atcgtaaaa aacgcattat ttattttcaa 540
gatgagggtc ctctgaccaa gaaactttgt gaacaagatt ccacatttga tgggtgact 600
gacaaacca tcttagactg ctgtgcctgc ggaactgcc agtacagact cacattttat 660
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314

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<212> DNA

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<213> Homo sapiens

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320

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<210> 310
 <211> 835
 <212> PRT
 <213> Homo sapiens

<400> 310

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Cys Ala Gly Gly Ser Gly Gln Asn Gln Pro Ser Leu Leu Pro Leu Leu
      35           40           45
Arg Arg Gly Pro Pro Leu Leu Ala Leu Leu Ser Phe Ala Trp Leu Ser
      50           55           60
Ser Ala Gln Leu Ser Ala Ala Pro Arg Pro Pro Ser Arg Gly Gly His
      65           70           75           80
Gly Leu Arg Val Ala Asp Ala Ser Ser Glu Leu Pro Leu Ser Ala Ala
      85           90           95
Pro Pro Pro Gly Arg Ala Phe Val Gly Thr Thr Ser Gly Arg Ser Arg
      100          105          110
Val Ala Lys Ala Cys Gly Arg Gly Thr Lys Leu Gly Ala Ala Lys Met
      115          120          125
Arg Leu Ser Pro Ala Pro Leu Lys Leu Ser Arg Thr Pro Ala Leu Leu
      130          135          140
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      145          150          155          160
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      165          170          175
Ala Gln Gly Thr Arg Arg Glu Gly Tyr Thr Glu Phe Ser Leu Arg Val
      180          185          190
Glu Gly Asp Pro Asp Phe Tyr Lys Pro Gly Thr Ser Tyr Arg Val Thr
      195          200          205
Leu Ser Ala Ala Pro Pro Ser Tyr Phe Arg Gly Phe Thr Leu Ile Ala
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Leu Arg Glu Asn Arg Glu Gly Asp Lys Glu Glu Asp His Ala Gly Thr
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Ser	Ile	Val	Gln	Lys	Arg	Ile	Tyr	Phe	Gln	Asp	Glu	Gly	Ser	Leu	
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Ser	Ile	Ser	Cys	Gly	Met	Gly	Met	Arg	Ser	Arg	Glu	Arg	Tyr	Val	Lys
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Glu	Lys	Cys	Thr	Val	Asn	Glu	Glu	Cys	Ser	Pro	Ser	Ser	Cys	Leu	Met
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322

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 Met Cys Lys Ala Glu Thr Ser Gln Ala Glu Lys Cys Met Met Pro Glu
 725 730 735
 Cys His Thr Ile Pro Cys Leu Leu Ser Pro Trp Ser Glu Trp Ser Asp
 740 745 750
 Cys Ser Val Thr Cys Gly Lys Gly Met Arg Thr Arg Gln Arg Met Leu
 755 760 765
 Lys Ser Leu Ala Glu Leu Gly Asp Cys Asn Glu Asp Leu Glu Gln Val
 770 775 780
 Glu Lys Cys Met Leu Pro Glu Cys Pro Ile Asp Cys Glu Leu Thr Glu
 785 790 795 800
 Trp Ser Gln Trp Ser Glu Cys Asn Lys Ser Cys Gly Lys Gly His Val
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<211> 3112

<212> DNA

<213> Homo sapiens

<400> 311

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<210> 312

<211> 782

<212> PRT

<213> Homo sapiens

<400> 312

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Lys His Gly Pro Gly Arg Trp Val Val Leu Ala Ala Val Leu Ile Gly
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Phe Val Ser Leu Ala Ser Lys Val Lys Asp Ala Leu Lys Leu Leu Tyr
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Ser Gly Val Pro Phe Leu Gly Pro Tyr His Lys Glu Ser Ala Val Thr
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145          150          155          160
Ile Pro Gln His Leu Val Glu Glu Ala Glu Arg Val Met Ala Glu Glu
165          170          175
Arg Val Val Met Leu Pro Pro Arg Ala Arg Ser Leu Lys Ser Phe Val
180          185          190
Val Thr Ser Val Val Ala Phe Pro Thr Asp Ser Lys Thr Val Gln Arg
195          200          205
Thr Gln Asp Asn Ser Cys Ser Phe Gly Leu His Ala Arg Gly Val Glu
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Leu Met Arg Phe Thr Thr Pro Gly Phe Pro Asp Ser Pro Tyr Pro Ala
225          230          235          240
His Ala Arg Cys Gln Trp Ala Leu Arg Gly Asp Ala Asp Ser Val Leu

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325

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326

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<210> 314

<211> 323

<212> PRT

<213> Homo sapiens

<400> 314

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Asn Cys Thr Cys Pro Thr Asn Lys Met Thr Val Cys Ser Pro Asp Gly
 35          40          45
Pro Gly Gly Arg Cys Gln Cys Arg Ala Leu Gly Ser Gly Met Ala Val
 50          55          60
Asp Cys Ser Thr Leu Thr Ser Lys Cys Leu Leu Leu Lys Ala Arg Met
 65          70          75          80
Ser Ala Pro Lys Asn Ala Arg Thr Leu Val Arg Pro Ser Glu His Ala
 85          90          95
Leu Val Asp Asn Asp Gly Leu Tyr Asp Pro Asp Cys Asp Pro Glu Gly
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Arg Phe Lys Ala Arg Gln Cys Asn Gln Thr Ser Val Cys Trp Cys Val
115          120          125
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130          135          140
Cys Asp Glu Leu Val Arg Thr His His Ile Leu Ile Asp Leu Arg His
145          150          155          160
Arg Pro Thr Ala Gly Ala Phe Asn His Ser Asp Leu Asp Ala Glu Leu
165          170          175
Arg Arg Leu Phe Arg Glu Arg Tyr Arg Leu His Pro Lys Phe Val Ala
180          185          190
Ala Val His Tyr Glu Gln Pro Thr Ile Gln Ile Glu Leu Arg Gln Asn
195          200          205
Thr Ser Gln Lys Ala Ala Gly Glu Val Asp Ile Gly Asp Ala Ala Tyr
210          215          220
Tyr Phe Glu Arg Asp Ile Lys Gly Glu Ser Leu Phe Gln Gly Arg Gly
225          230          235          240
Gly Leu Asp Leu Arg Val Arg Gly Glu Pro Leu Gln Val Glu Arg Thr
245          250          255
Leu Ile Tyr Tyr Leu Asp Glu Ile Pro Pro Lys Phe Ser Met Lys Arg
260          265          270
Leu Thr Ala Gly Leu Ile Ala Val Ile Val Val Val Val Val Ala Leu
275          280          285
Val Ala Gly Met Ala Val Leu Val Ile Thr Asn Arg Arg Lys Ser Gly
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<210> 315

327

<211> 1142

<212> DNA

<213> Homo sapiens

<400> 315

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<210> 316

<211> 235

<212> PRT

<213> Homo sapiens

<400> 316

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 20          25          30
Ala Glu Ile Cys Leu Leu Pro Leu Asp Tyr Gly Pro Cys Arg Ala Leu
 35          40          45
Leu Leu Arg Tyr Tyr Tyr Asp Arg Tyr Thr Gln Ser Cys Arg Gln Phe
 50          55          60
Leu Tyr Gly Gly Cys Glu Gly Asn Ala Asn Asn Phe Tyr Thr Trp Glu
 65          70          75          80
Ala Cys Asp Asp Ala Cys Trp Arg Ile Glu Lys Val Pro Lys Val Cys
 85          90          95
Arg Leu Gln Val Ser Val Asp Asp Gln Cys Glu Gly Ser Thr Glu Lys
100          105          110
Tyr Phe Phe Asn Leu Ser Ser Met Thr Cys Glu Lys Phe Phe Ser Gly
115          120          125
Gly Cys His Arg Asn Arg Ile Glu Asn Arg Phe Pro Asp Glu Ala Thr
130          135          140
Cys Met Gly Phe Cys Ala Pro Lys Lys Ile Pro Ser Phe Cys Tyr Ser
145          150          155          160
Pro Lys Asp Glu Gly Leu Cys Ser Ala Asn Val Thr Arg Tyr Tyr Phe
165          170          175
Asn Pro Arg Tyr Arg Thr Cys Asp Ala Phe Thr Tyr Thr Gly Cys Gly
180          185          190
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328

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 225 230 235

<210> 317
 <211> 2307
 <212> DNA
 <213> Homo sapiens

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<210> 318

329

<211> 428
 <212> PRT
 <213> Homo sapiens

<400> 318

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			20					25					30		
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Pro	Glu	Gly	Pro	Ala	Val	Ala	Val	Arg	Leu	Ser	Lys	Asp	Arg	Ser	Thr
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Leu	Thr	Ala	Ala	His	Cys	Phe	Arg	Lys	His	Thr	Asp	Val	Phe	Asn	Trp
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Lys	Val	Arg	Ala	Gly	Ser	Asp	Lys	Leu	Gly	Ser	Phe	Pro	Ser	Leu	Ala
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Val	Ala	Lys	Ile	Ile	Ile	Ile	Glu	Phe	Asn	Pro	Met	Tyr	Pro	Lys	Asp
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Gly	Lys	Met	Ser	Asp	Ile	Leu	Leu	Gln	Ala	Ser	Val	Gln	Val	Ile	Asp
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Ser	Thr	Arg	Cys	Asn	Ala	Asp	Asp	Ala	Tyr	Gln	Gly	Glu	Val	Thr	Glu
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Lys	Met	Met	Cys	Ala	Gly	Ile	Pro	Glu	Gly	Gly	Val	Asp	Thr	Cys	Gln
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Gly	Asp	Ser	Gly	Gly	Pro	Leu	Met	Tyr	Gln	Ser	Asp	Gln	Trp	His	Val
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Val	Gly	Ile	Val	Ser	Trp	Gly	Tyr	Gly	Cys	Gly	Gly	Pro	Ser	Thr	Pro
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420

425

<210> 319
 <211> 3529
 <212> DNA
 <213> Homo sapiens

<400> 319

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331

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<210> 320

<211> 444

<212> PRT

<213> Homo sapiens

<400> 320

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Lys Ala Leu Lys Ile Phe Gln Glu Lys His Val Asn Leu Leu His Ile
      35           40           45
Glu Ser Arg Lys Ser Lys Arg Arg Asn Ser Glu Phe Glu Ile Phe Val
      50           55           60
Asp Cys Asp Ile Asn Arg Glu Gln Leu Asn Asp Ile Phe His Leu Leu
      65           70           75           80
Lys Ser His Thr Asn Val Leu Ser Val Asn Leu Pro Asp Asn Phe Thr
      85           90           95
Leu Lys Glu Asp Gly Met Glu Thr Val Pro Trp Phe Pro Lys Lys Ile
      100          105          110
Ser Asp Leu Asp His Cys Ala Asn Arg Val Leu Met Tyr Gly Ser Glu
      115          120          125
Leu Asp Ala Asp His Pro Gly Phe Lys Asp Asn Val Tyr Arg Lys Arg
      130          135          140
Arg Lys Tyr Phe Ala Asp Leu Ala Met Asn Tyr Lys His Gly Asp Pro
      145          150          155          160
Ile Pro Lys Val Glu Phe Thr Glu Glu Glu Ile Lys Thr Trp Gly Thr
      165          170          175
Val Phe Gln Glu Leu Asn Lys Leu Tyr Pro Thr His Ala Cys Arg Glu
      180          185          190
Tyr Leu Lys Asn Leu Pro Leu Leu Ser Lys Tyr Cys Gly Tyr Arg Glu
      195          200          205
Asp Asn Ile Pro Gln Leu Glu Asp Val Ser Asn Phe Leu Lys Glu Arg
      210          215          220
Thr Gly Phe Ser Ile Arg Pro Val Ala Gly Tyr Leu Ser Pro Arg Asp
      225          230          235          240
Phe Leu Ser Gly Leu Ala Phe Arg Val Phe His Cys Thr Gln Tyr Val
      245          250          255
Arg His Ser Ser Asp Pro Phe Tyr Thr Pro Glu Pro Asp Thr Cys His
      260          265          270
Glu Leu Leu Gly His Val Pro Leu Leu Ala Glu Pro Ser Phe Ala Gln
      275          280          285
Phe Ser Gln Glu Ile Gly Leu Ala Ser Leu Gly Ala Ser Glu Glu Ala
      290          295          300
Val Gln Lys Leu Ala Thr Cys Tyr Phe Phe Thr Val Glu Phe Gly Leu
      305          310          315          320
Cys Lys Gln Asp Gly Gln Leu Arg Val Phe Gly Ala Gly Leu Leu Ser

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<210> 321
<211> 3505
<212> DNA
<213> Homo sapiens
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<210> 322

<211> 466

<212> PRT

<213> Homo sapiens

<400> 322

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Met Ile Glu Asp Asn Lys Glu Asn Lys Asp His Ser Leu Glu Arg Gly
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Arg Ala Ser Leu Ile Phe Ser Leu Lys Asn Glu Val Gly Gly Leu Ile
          20          25          30
Lys Ala Leu Lys Ile Phe Gln Glu Lys His Val Asn Leu Leu His Ile
          35          40          45
Glu Ser Arg Lys Ser Lys Arg Arg Asn Ser Glu Phe Glu Ile Phe Val
          50          55          60
Asp Cys Asp Ile Asn Arg Glu Gln Leu Asn Asp Ile Phe His Leu Leu
65          70          75          80
Lys Ser His Thr Asn Val Leu Ser Val Asn Leu Pro Asp Asn Phe Thr
          85          90          95
Leu Lys Glu Asp Gly Met Glu Thr Val Pro Trp Phe Pro Lys Lys Ile
          100         105         110
Ser Asp Leu Asp His Cys Ala Asn Arg Val Leu Met Tyr Gly Ser Glu
          115         120         125
Leu Asp Ala Asp His Pro Gly Phe Lys Asp Asn Val Tyr Arg Lys Arg
          130         135         140
Arg Lys Tyr Phe Ala Asp Leu Ala Met Asn Tyr Lys His Gly Asp Pro
145         150         155         160
Ile Pro Lys Val Glu Phe Thr Glu Glu Glu Ile Lys Thr Trp Gly Thr
          165         170         175
Val Phe Gln Glu Leu Asn Lys Leu Tyr Pro Thr His Ala Cys Arg Glu
          180         185         190
Tyr Leu Lys Asn Leu Pro Leu Leu Ser Lys Tyr Cys Gly Tyr Arg Glu
          195         200         205
Asp Asn Ile Pro Gln Leu Glu Asp Val Ser Asn Phe Leu Lys Glu Arg

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334

210	215	220
Thr Gly Phe Ser Ile Arg	Pro Val Ala Gly Tyr	Leu Ser Pro Arg Asp
225	230	235
Phe Leu Ser Gly Leu Ala	Phe Arg Val Phe His	Cys Thr Gln Tyr Val
245	250	255
Arg His Ser Ser Asp	Pro Phe Tyr Thr	Pro Glu Pro Asp Thr Cys His
260	265	270
Glu Leu Leu Gly His Val	Pro Leu Leu Ala Glu	Pro Ser Phe Ala Gln
275	280	285
Phe Ser Gln Glu Ile Gly	Leu Ala Ser Leu Gly	Ala Ser Glu Glu Ala
290	295	300
Val Gln Lys Leu Ala Thr	Cys Tyr Phe Phe Thr	Val Glu Phe Gly Leu
305	310	315
Cys Lys Gln Asp Gly	Gln Leu Arg Val Phe	Gly Ala Gly Leu Leu Ser
325	330	335
Ser Ile Ser Glu Leu Lys	His Ala Leu Ser Gly	His Ala Lys Val Lys
340	345	350
Pro Phe Asp Pro Lys Ile	Thr Cys Lys Gln Glu	Cys Leu Ile Thr Thr
355	360	365
Phe Gln Asp Val Tyr Phe	Val Ser Glu Ser Phe	Glu Asp Ala Lys Glu
370	375	380
Lys Met Arg Glu Phe Thr	Lys Thr Ile Lys Arg	Pro Phe Gly Val Lys
385	390	395
Tyr Asn Pro Tyr Thr Arg	Ser Ile Gln Ile Leu	Lys Asp Thr Lys Ser
405	410	415
Ile Thr Ser Ala Met Asn	Glu Leu Gln His Asp	Leu Asp Val Val Ser
420	425	430
Asp Ala Leu Ala Lys Ser	Leu Asn Glu Asp Val	Leu Gln Val Ser Val
435	440	445
Phe Ala Leu Leu Leu Phe	Leu Pro Ser Leu His	Gly Glu Cys His Pro
450	455	460
Asp Thr		
465		

<210> 323
 <211> 1154
 <212> DNA
 <213> Homo sapiens

<400> 323
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 accatgcagt gcttcagctt cattaagacc atgatgatcc tcttcaattt gctcatcttt 180
 ctgtgtggtg cagccctggt ggcagtgggc atctgggtgt caatcgatgg ggcacccctt 240
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335

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 aaaaaaaaaa aagt 1154

<210> 324
 <211> 258
 <212> PRT
 <213> Homo sapiens

<400> 324
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 20 25 30
 Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser
 35 40 45
 Ser Ala Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly
 50 55 60
 Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr
 65 70 75 80
 Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Leu Ile
 85 90 95
 Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr
 100 105 110
 Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys
 115 120 125
 Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
 130 135 140
 Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
 145 150 155 160
 Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
 165 170 175
 Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
 180 185 190
 His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
 195 200 205
 Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
 210 215 220
 Leu Glu Phe Phe Ser Asn Ser Ala Arg Arg Pro Pro Leu Pro Glu Ser
 225 230 235 240
 Leu Tyr Ser Thr Pro Ile Arg Arg Asp His Val Phe Leu Gln Pro Ser
 245 250 255
 Pro Pro

<210> 325
 <211> 1076
 <212> DNA
 <213> Homo sapiens

<400> 325
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 aagatcttcg ggccactgtc gtccagtgcc atgcagtttg tcaacgtggg ctacttcctc 180
 atcgagcccg gcgttgtggc ctttgctctt ggtttcctgg gctgctatgg tgctaagact 240
 gagagcaagt gtgccctcgt gacgttcttc ttcacccctc tcctcatctt cattgctgag 300
 gttgcagctg ctgtgggtgc cttgggtgtac accacaatgg ctgagcactt cctgacgttg 360

336

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ctggtagtgc ctgccatcaa gaaagattat ggttcccagg aagacttcac tcaagtgtgg 420
aacaccacca tgaaagggct caagtgtctgt ggcttcacca actatacggg ttttgaggac 480
tcaccctact tcaaagagaa cagtgccttt ccccccattct gttgcaatga caacgtcacc 540
aacacagcca atgaaacctg caccgagcaa aagggtcacg accaaaaagt agaggggttg 600
ttcaatcagc ttttgtatga catccgaact aatgcagtca ccgtgggtgg tgtggcagct 660
ggaattgggg gcctcgagct ggctgccatg attgtgtcca tgtatctgta ctgcaatcta 720
caataagtcc acttctgcct ctgccactac tgctgccaca tgggaactgt gaagaggcac 780
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agccagttct gttgccattt ccccagttct attaaaccct tgatatgccc cctaggccta 1020
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<210> 326

<211> 241

<212> PRT

<213> Homo sapiens

<400> 326

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Met Gln Cys Phe Ser Phe Ile Lys Thr Met Met Ile Leu Phe Asn Leu
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20      25      30
Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser
35      40      45
Ser Ala Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly
50      55      60
Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr
65      70      75      80
Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Leu Ile
85      90      95
Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr
100     105     110
Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys
115     120     125
Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
130     135     140
Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
145     150     155     160
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
165     170     175
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Glu Gln Lys Ala
180     185     190
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
195     200     205
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
210     215     220
Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu
225     230     235     240
Gln

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<210> 327

<211> 2244

<212> DNA

<213> Homo sapiens

<400> 327

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ttctcaggat ctcaacaagg aagagcagac caagggttgc tctgattcct tacaaccttc 180
cgtaattcca ggcttgtggc cccaaattca gggcccacc cttccaggaa caaatcatta 240
tagtaataat ttgccttcat cttccatata ccaactaagc atgtttaact acgaacgtcc 300
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caaggacacc cttcttcata atggaaatca acgtctaaca tatgaagaga agatggctcg 840
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gcttgtaata acgtttactg gtactgcttt ctaaatactg ttttaccgt tttctctgt 2160
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aaaattcaaa tatttaaaac ggac 2244

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<210> 328

<211> 498

<212> PRT

<213> Homo sapiens

<400> 328

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Met Phe Asn Tyr Glu Arg Pro Lys His Phe Ile Gln Ser Gln Asn Pro
  1           5           10          15
Cys Gly Ser Arg Leu Gln Pro Pro Gly Pro Glu Thr Ser Ser Phe Ser
          20          25          30
Ser Gln Thr Lys Gln Ser Ser Ile Ile Ile Gln Pro Arg Gln Cys Thr
          35          40          45
Glu Gln Arg Phe Ser Ala Ser Ser Thr Leu Ser Ser His Ile Thr Met
          50          55          60
Ser Ser Ser Ala Phe Pro Ala Ser Pro Gln Gln His Ala Gly Ser Asn
          65          70          75          80
Pro Gly Gln Arg Val Thr Thr Thr Tyr Asn Gln Ser Pro Ala Ser Phe
          85          90          95

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338

Leu Ser Ser Ile Leu Pro Ser Gln Pro Asp Tyr Asn Ser Ser Lys Ile
 100 105 110
 Pro Ser Ala Met Asp Ser Asn Tyr Gln Gln Ser Ser Ala Gly Gln Pro
 115 120 125
 Ile Asn Ala Lys Pro Ser Gln Thr Ala Asn Ala Lys Pro Ile Pro Arg
 130 135 140
 Thr Pro Asp His Glu Ile Gln Gly Ser Lys Glu Ala Leu Ile Gln Asp
 145 150 155 160
 Leu Glu Arg Lys Leu Lys Cys Lys Asp Thr Leu Leu His Asn Gly Asn
 165 170 175
 Gln Arg Leu Thr Tyr Glu Glu Lys Met Ala Arg Arg Leu Leu Gly Pro
 180 185 190
 Gln Asn Ala Ala Val Phe Gln Ala Gln Asp Asp Ser Gly Ala Gln
 195 200 205
 Asp Ser Gln Gln His Asn Ser Glu His Ala Arg Leu Gln Val Pro Thr
 210 215 220
 Ser Gln Val Arg Ser Arg Ser Thr Ser Arg Gly Asp Val Asn Asp Gln
 225 230 235 240
 Asp Ala Ile Gln Glu Lys Phe Tyr Pro Pro Arg Phe Ile Gln Val Pro
 245 250 255
 Glu Asn Met Ser Ile Asp Glu Gly Arg Phe Cys Arg Met Asp Phe Lys
 260 265 270
 Val Ser Gly Leu Pro Ala Pro Asp Val Ser Trp Tyr Leu Asn Gly Arg
 275 280 285
 Thr Val Gln Ser Asp Asp Leu His Lys Met Ile Val Ser Glu Lys Gly
 290 295 300
 Leu His Ser Leu Ile Phe Glu Val Val Arg Ala Ser Asp Ala Gly Ala
 305 310 315 320
 Tyr Ala Cys Val Ala Lys Asn Arg Ala Gly Glu Ala Thr Phe Thr Val
 325 330 335
 Gln Leu Asp Val Leu Ala Lys Glu His Lys Arg Ala Pro Met Phe Ile
 340 345 350
 Tyr Lys Pro Gln Ser Lys Lys Val Leu Glu Gly Asp Ser Val Lys Leu
 355 360 365
 Glu Cys Gln Ile Ser Ala Ile Pro Pro Pro Lys Leu Phe Trp Lys Arg
 370 375 380
 Asn Asn Glu Met Val Gln Phe Asn Thr Asp Arg Ile Ser Leu Tyr Gln
 385 390 395 400
 Asp Asn Thr Gly Arg Val Thr Leu Leu Ile Lys Asp Val Asn Lys Lys
 405 410 415
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 Pro Ala Pro Lys Gln Leu Arg Val Arg Pro Thr Phe Ser Lys Tyr Leu
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<210> 329

<211> 3649

<212> DNA

<213> Homo sapiens

<400> 329

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340

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<210> 330

<211> 812

<212> PRT

<213> Homo sapiens

<400> 330

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Pro Ser Pro Ser Gln Gly Thr Leu Ser Ala His Pro Leu Gly Leu Ser
          50           55           60
Ala Ser Pro Arg Leu Ala Ala Arg Glu Gly Gln Arg Phe Ser Leu Ser
65           70           75           80
Leu His Ser Glu Ser Lys Val Leu Ile Leu Phe Cys Asn Leu Val Gly
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Ser Gly Gln Gln Ala Ser Arg Phe Gly Pro Pro Phe Leu Ile Arg Glu
          100          105          110
Asp Arg Ala Val Ser Trp Ala Gln Leu Gln Gln Ser Ile Leu Ser Lys
          115          120          125
Val Arg His Leu Met Lys Ser Glu Ala Pro Val Gln Asn Leu Gly Ser
          130          135          140
Leu Phe Ser Ile Arg Val Val Gly Leu Ser Val Ala Cys Ser Tyr Leu
145          150          155          160
Ser Pro Lys Asp Ser Arg Pro Leu Cys His Trp Ala Val Asp Arg Val
          165          170          175
Leu His Leu Arg Arg Pro Gly Gly Pro Pro His Val Lys Leu Ala Val
          180          185          190
Glu Trp Asp Ser Ser Val Lys Glu Arg Leu Phe Gly Ser Leu Gln Glu
          195          200          205
Glu Arg Ala Gln Asp Ala Asp Ser Val Trp Gln Gln Gln Gln Ala His
          210          215          220
Gln Gln His Ser Cys Thr Leu Asp Glu Cys Phe Gln Phe Tyr Thr Lys
225          230          235          240
Glu Glu Gln Leu Ala Gln Asp Asp Ala Trp Lys Cys Pro His Cys Gln
          245          250          255
Val Leu Gln Gln Gly Met Val Lys Leu Ser Leu Trp Thr Leu Pro Asp
          260          265          270
Ile Leu Ile Ile His Leu Lys Arg Phe Cys Gln Val Gly Glu Arg Arg
          275          280          285
Asn Lys Leu Ser Thr Leu Val Lys Phe Pro Leu Ser Gly Leu Asn Met
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Leu Gln Gly Gly His Tyr Thr Ala Tyr Cys Arg Asn Ser Leu Asp Gly
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 405 410 415
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 420 425 430
 Ser Thr Arg Gly Ser Leu Leu Ser Trp Ser Ser Ala Pro Cys Pro Ser
 435 440 445
 Leu Pro Gln Val Pro Asp Ser Pro Ile Phe Thr Asn Ser Leu Cys Asn
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 485 490 495
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 Arg Arg Pro Arg Ser Thr Ser Gln Ser Ile Val Ser Leu Leu Thr Gly
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 595 600 605
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 675 680 685
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 755 760 765
 Pro Arg Gly Ser Ala Leu Gly Met Ser Gln Arg Thr Val Pro Gly Glu
 770 775 780
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342

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 <211> 1811
 <212> DNA
 <213> Homo sapiens

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<210> 332
 <211> 282
 <212> PRT
 <213> Homo sapiens

<400> 332
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 Gly Glu Asp Gly Ile Gln Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu
 50 55 60
 Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val
 65 70 75 80
 His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met
 85 90 95
 Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn
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343

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	130					135					140				
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Ala	Ser	Ser	Glu	Thr	Leu	Arg	Cys	Glu	Ala	Pro	Arg	Trp	Phe	Pro	Gln
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Pro	Thr	Val	Val	Trp	Ala	Ser	Gln	Val	Asp	Gln	Gly	Ala	Asn	Phe	Ser
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Glu	Val	Ser	Asn	Thr	Ser	Phe	Glu	Leu	Asn	Ser	Glu	Asn	Val	Thr	Met
	195						200					205			
Lys	Val	Val	Ser	Val	Leu	Tyr	Asn	Val	Thr	Ile	Asn	Asn	Thr	Tyr	Ser
	210					215					220				
Cys	Met	Ile	Glu	Asn	Asp	Ile	Ala	Lys	Ala	Thr	Gly	Asp	Ile	Lys	Val
225					230					235					240
Thr	Glu	Ser	Glu	Ile	Lys	Arg	Arg	Ser	His	Leu	Gln	Leu	Leu	Asn	Ser
				245					250					255	
Lys	Ala	Ser	Leu	Cys	Val	Ser	Ser	Phe	Phe	Ala	Ile	Ser	Trp	Ala	Leu
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<210> 333
 <211> 1984
 <212> DNA
 <213> Homo sapiens

<400> 333

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344

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<210> 334

<211> 258

<212> PRT

<213> Homo sapiens

<400> 334

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			20					25					30		
Lys	Leu	Asp	Thr	Ser	Gly	Phe	Ser	Ser	Ile	Leu	Val	Thr	Leu	Thr	Lys
		35					40					45			
Ala	Ala	Val	Ala	Leu	Lys	Met	Gly	Asp	Leu	Asp	Met	His	Arg	Asn	Glu
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Met	Lys	Ser	His	Ser	Glu	Met	Lys	Leu	Val	Cys	Gly	Phe	Ile	Leu	Glu
65					70				75					80	
Pro	Arg	Leu	Leu	Ile	Gln	Gln	Arg	Lys	Gly	Gln	Ile	Val	Pro	Thr	Glu
			85					90						95	
Leu	Ala	Leu	His	Leu	Lys	Glu	Thr	Gln	Pro	Gly	Leu	Leu	Val	Ala	Ser
			100					105					110		
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		115				120						125			
Ser	Phe	Phe	Lys	Val	Leu	Cys	Ala	Lys	Asp	Glu	Asp	Thr	Ile	Pro	Gln
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			165					170					175		
Arg	Leu	Ser	Lys	Arg	Gln	Pro	Pro	Asp	Thr	Thr	Pro	Leu	Arg	Thr	Ser
			180					185					190		
Glu	Asp	Leu	Ile	Asn	Ala	Cys	Ser	His	Tyr	Gly	Leu	Ile	Tyr	Pro	Trp
	195					200					205				
Val	His	Val	Val	Ile	Ser	Ser	Asp	Ser	Leu	Ala	Asp	Lys	Asn	Tyr	Thr
	210				215						220				
Glu	Asp	Leu	Ser	Lys	Leu	Gln	Leu	Pro	Leu	Phe	Arg	Ser	Trp	Ser	His
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His Ala

<210> 335

<211> 2180

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(2180)

<223> n = A,T,C or G

<400> 335

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<210> 336

<211> 234

<212> PRT

<213> Homo sapiens

<400> 336

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20          25          30
Arg Arg Lys Leu Leu Met Asn Ser Glu Gln Arg Ile Asn Arg Ile Met
35          40          45
Gly Phe His Arg Pro Gly Ser Gly Ala Glu Glu Glu Ser Gln Thr Lys
50          55          60
Ser Lys Gln Gln Asp Ser Asp Lys Leu Asn Ser Leu Ser Val Pro Ser
65          70          75          80
Val Ser Lys Arg Val Val Leu Gly Asp Ser Val Ser Thr Gly Thr Thr
85          90          95

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Asp Gln Gln Gly Gly Val Ala Glu Val Lys Gly Thr Gln Leu Gly Asp
 100 105 110
 Lys Leu Asp Ser Phe Ile Lys Pro Pro Glu Cys Ser Ser Asp Val Asn
 115 120 125
 Leu Glu Leu Arg Gln Arg Asn Arg Gly Asp Leu Thr Ala Asp Ser Val
 130 135 140
 Gln Arg Gly Ser Arg His Gly Leu Glu Gln Tyr Leu Ser Arg Phe Glu
 145 150 155 160
 Glu Ala Met Lys Leu Arg Lys Gln Leu Ile Ser Glu Lys Pro Ser Gln
 165 170 175
 Glu Asp Gly Asn Thr Thr Glu Glu Phe Asp Ser Phe Arg Ile Phe Arg
 180 185 190
 Leu Val Gly Cys Ala Leu Leu Ala Leu Gly Val Arg Ala Phe Val Cys
 195 200 205
 Lys Tyr Leu Ser Ile Phe Ala Pro Phe Leu Thr Leu Gln Leu Ala Leu
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 His Gly Ile Ile Gln Ile Phe Ser Gln Glu
 225 230

<210> 337
 <211> 3695
 <212> DNA
 <213> Homo sapiens

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<210> 338

<211> 353

<212> PRT

<213> Homo sapiens

<400> 338

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          20          25          30
Val Leu Cys Val Gly Thr Phe Phe Cys Leu Phe Ile Phe Phe Ser Asn
          35          40          45
Ser Leu Val Ile Ala Ala Val Ile Lys Asn Arg Lys Phe His Phe Pro
          50          55          60
Phe Tyr Tyr Leu Leu Ala Asn Leu Ala Ala Ala Asp Phe Phe Ala Gly
65          70          75          80
Ile Ala Tyr Val Phe Leu Met Phe Asn Thr Gly Pro Val Ser Lys Thr
          85          90          95
Leu Thr Val Asn Arg Trp Phe Leu Arg Gln Gly Leu Leu Asp Ser Ser
          100          105          110
Leu Thr Ala Ser Leu Thr Asn Leu Leu Val Ile Ala Val Glu Arg His
          115          120          125
Met Ser Ile Met Arg Met Arg Val His Ser Asn Leu Thr Lys Lys Arg
          130          135          140
Val Thr Leu Leu Ile Leu Leu Val Trp Ala Ile Ala Ile Phe Met Gly
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348

[illegible]

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<210> 339
<211> 3320
<212> DNA
<213> Homo sapiens
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<400> 339							
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c	t	g	t	g	c	t	360
a	a	g	g	a	a	g	420
t	t	t	g	a	g	a	480
g	g	g	c	a	g	g	540
a	t	t	g	t	c	c	600
g	a	c	t	c	g	a	660
g	g	c	t	c	g	t	720
a	a	a	c	t	g	c	780
a	g	c	a	c	a	a	840
t	t	c	a	c	c	c	900
a	a	c	a	c	c	t	960
a	t	t	g	t	c	a	1020
a	c	t	g	g	c	a	1080
c	t	g	t	c	c	c	1140
c	t	g	t	c	c	a	1200
c	a	g	a	g	c	t	1260
g	t	g	c	a	a	g	1320
g	c	c	c	g	g	c	1380
c	t	g	a	c	g	g	1440
a	t	g	a	c	a	c	1500


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aaaaaaaaa aaaaaaaaaa 3320

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<210> 340

<211> 784

<212> PRT

<213> Homo sapiens

<400> 340

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20          25          30
Asp Gln Phe Trp Ala Asp Thr Ala Thr Ser Val Gln Asp Val Phe Ala
35          40          45
Leu Val Pro Ala Ala Glu Ile Arg Ala Val Arg Glu Glu Ser Pro Ser
50          55          60
Asn Leu Ala Thr Leu Cys Tyr Lys Ala Val Glu Lys Leu Val Gln Gly
65          70          75          80
Ala Glu Ser Gly Cys His Ser Glu Lys Glu Lys Gln Ile Val Leu Asn
85          90          95
Cys Ser Arg Leu Leu Thr Arg Val Leu Pro Tyr Ile Phe Glu Asp Pro
100         105         110
Asp Trp Arg Gly Phe Phe Trp Ser Thr Val Pro Gly Ala Gly Arg Gly
115         120         125
Gly Gln Gly Glu Glu Asp Asp Glu His Ala Arg Pro Leu Ala Glu Ser
130         135         140
Leu Leu Leu Ala Ile Ala Asp Leu Leu Phe Cys Pro Asp Thr Gln Ser
145         150         155         160

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350

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Ser	Cys	Glu	Tyr	Ile	Trp	Glu	Ala	Gly	Val	Gly	Phe	Ala	His	Ser	Pro
			180					185					190		
Gln	Pro	Asn	Tyr	Ile	His	Asp	Met	Asn	Arg	Met	Glu	Leu	Leu	Lys	Leu
		195					200					205			
Leu	Leu	Thr	Cys	Phe	Ser	Glu	Ala	Met	Tyr	Leu	Pro	Pro	Ala	Pro	Glu
	210					215					220				
Ser	Gly	Ser	Thr	Asn	Pro	Trp	Val	Gln	Phe	Phe	Cys	Ser	Thr	Glu	Asn
225				230						235					240
Arg	His	Ala	Leu	Pro	Leu	Phe	Thr	Ser	Leu	Leu	Asn	Thr	Val	Cys	Ala
				245					250					255	
Tyr	Asp	Pro	Val	Gly	Tyr	Gly	Ile	Pro	Tyr	Asn	His	Leu	Leu	Phe	Ser
			260					265					270		
Asp	Tyr	Arg	Glu	Pro	Leu	Val	Glu	Ala	Gln	Val	Leu	Ile	Val	Thr	Leu
		275					280					285			
Asp	His	Asp	Ser	Ala	Ser	Ser	Ala	Ser	Pro	Thr	Val	Asp	Gly	Thr	Thr
	290					295					300				
Thr	Gly	Thr	Ala	Met	Asp	Asp	Ala	Asp	Pro	Pro	Gly	Pro	Glu	Asn	Leu
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Phe	Val	Asn	Tyr	Leu	Ser	Arg	Ile	His	Arg	Glu	Glu	Asp	Phe	Gln	Phe
			325						330					335	
Ile	Leu	Lys	Gly	Ile	Ala	Arg	Leu	Leu	Ser	Asn	Pro	Leu	Leu	Gln	Thr
	340							345					350		
Tyr	Leu	Pro	Asn	Ser	Thr	Lys	Lys	Ile	Gln	Phe	His	Gln	Glu	Leu	Leu
	355					360						365			
Val	Leu	Phe	Trp	Lys	Leu	Cys	Asp	Phe	Asn	Lys	Lys	Phe	Leu	Phe	Phe
	370					375					380				
Val	Leu	Lys	Ser	Ser	Asp	Val	Leu	Asp	Ile	Leu	Val	Pro	Ile	Leu	Phe
385					390					395					400
Phe	Leu	Asn	Asp	Ala	Arg	Ala	Asp	Gln	Ser	Arg	Val	Gly	Leu	Met	His
			405					410						415	
Ile	Gly	Val	Phe	Ile	Leu	Leu	Leu	Leu	Ser	Gly	Glu	Arg	Asn	Phe	Gly
		420						425					430		
Val	Arg	Leu	Asn	Lys	Pro	Tyr	Ser	Ile	Arg	Val	Pro	Met	Asp	Ile	Pro
		435					440					445			
Val	Phe	Thr	Gly	Thr	His	Ala	Asp	Leu	Leu	Ile	Val	Val	Phe	His	Lys
	450					455					460				
Ile	Ile	Thr	Ser	Gly	His	Gln	Arg	Leu	Gln	Pro	Leu	Phe	Asp	Cys	Leu
465					470					475					480
Leu	Thr	Ile	Val	Val	Asn	Val	Ser	Pro	Tyr	Leu	Lys	Ser	Leu	Ser	Met
			485						490					495	
Val	Thr	Ala	Asn	Lys	Leu	Leu	His	Leu	Leu	Glu	Ala	Phe	Ser	Thr	Thr
			500					505					510		
Trp	Phe	Leu	Phe	Ser	Ala	Ala	Gln	Asn	His	His	Leu	Val	Phe	Phe	Leu
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Asn	Leu	Val	Tyr	Ala	Ile	Ile	Arg	Lys	Arg	Ser	Ile	Phe	His	Gln	Leu
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Ala	Asn	Leu	Pro	Thr	Asp	Pro	Pro	Thr	Ile	His	Lys	Ala	Leu	Gln	Arg
			565					570						575	
Arg	Arg	Arg	Thr	Pro	Glu	Pro	Leu	Ser	Arg	Thr	Gly	Ser	Gln	Glu	Gly
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Thr	Ser	Met	Glu	Gly	Ser	Arg	Pro	Ala	Ala	Pro	Ala	Glu	Pro	Gly	Thr
	595						600					605			
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	610					615					620				

351

Lys Ser Gln Val Ser Glu Asp Gly Thr Leu Arg Ser Leu Glu Pro Glu
 625 630 635 640
 Pro Gln Gln Ser Leu Glu Asp Gly Ser Pro Ala Lys Gly Glu Pro Ser
 645 650 655
 Gln Ala Trp Arg Glu Gln Arg Arg Pro Ser Thr Ser Ser Ala Ser Gly
 660 665 670
 Gln Trp Ser Pro Thr Pro Glu Trp Val Leu Ser Trp Lys Ser Lys Leu
 675 680 685
 Pro Leu Gln Thr Ile Met Arg Leu Leu Gln Val Leu Val Pro Gln Val
 690 695 700
 Glu Lys Ile Cys Ile Asp Lys Gly Leu Thr Asp Glu Ser Glu Ile Leu
 705 710 715 720
 Arg Phe Leu Gln His Gly Thr Leu Val Gly Leu Leu Pro Val Pro His
 725 730 735
 Pro Ile Leu Ile Arg Lys Tyr Gln Ala Asn Ser Gly Thr Ala Met Trp
 740 745 750
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 755 760 765
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 770 775 780

<210> 341
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 <212> DNA
 <213> Homo sapiens

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<210> 342
 <211> 788
 <212> PRT
 <213> Homo sapiens

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 35 40 45
 Leu Val Pro Ala Ala Glu Ile Arg Ala Val Arg Glu Glu Ser Pro Ser
 50 55 60
 Asn Leu Ala Thr Leu Cys Tyr Lys Ala Val Glu Lys Leu Val Gln Gly
 65 70 75 80
 Ala Glu Ser Gly Cys His Ser Glu Lys Glu Lys Gln Ile Val Leu Asn
 85 90 95
 Cys Ser Arg Leu Leu Thr Arg Val Leu Pro Tyr Ile Phe Glu Asp Pro
 100 105 110
 Asp Trp Arg Gly Phe Phe Trp Ser Thr Val Pro Gly Ala Gly Arg Gly
 115 120 125
 Gly Gln Gly Glu Glu Asp Asp Glu His Ala Arg Pro Leu Ala Glu Ser
 130 135 140
 Leu Leu Leu Ala Ile Ala Asp Leu Leu Phe Cys Pro Asp Phe Thr Val
 145 150 155 160
 Gln Ser His Arg Arg Ser Thr Val Asp Ser Ala Glu Asp Val His Ser
 165 170 175
 Leu Asp Ser Cys Glu Tyr Ile Trp Glu Ala Gly Val Gly Phe Ala His
 180 185 190
 Ser Pro Gln Pro Asn Tyr Ile His Asp Met Asn Arg Met Glu Leu Leu

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Lys	Leu	Leu	Leu	Thr	Cys	Phe	Ser	Glu	Ala	Met	Tyr	Leu	Pro	Pro	Ala		
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Pro	Glu	Ser	Gly	Ser	Thr	Asn	Pro	Trp	Val	Gln	Phe	Phe	Cys	Ser	Thr		
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Cys	Ala	Tyr	Asp	Pro	Val	Gly	Tyr	Gly	Ile	Pro	Tyr	Asn	His	Leu	Leu		
			260					265					270				
Phe	Ser	Asp	Tyr	Arg	Glu	Pro	Leu	Val	Glu	Glu	Ala	Ala	Gln	Val	Leu		
			275				280						285				
Ile	Val	Thr	Leu	Asp	His	Asp	Ser	Ala	Ser	Ser	Ala	Ser	Pro	Thr	Val		
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Asp	Gly	Thr	Thr	Thr	Gly	Thr	Ala	Met	Asp	Asp	Ala	Asp	Pro	Pro	Gly		
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Pro	Glu	Asn	Leu	Phe	Val	Asn	Tyr	Leu	Ser	Arg	Ile	His	Arg	Glu	Glu		
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Asp	Phe	Gln	Phe	Ile	Leu	Lys	Gly	Ile	Ala	Arg	Leu	Leu	Ser	Asn	Pro		
			340				345						350				
Leu	Leu	Gln	Thr	Tyr	Leu	Pro	Asn	Ser	Thr	Lys	Lys	Ile	Gln	Phe	His		
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Gln	Glu	Leu	Leu	Val	Leu	Phe	Trp	Lys	Leu	Cys	Asp	Phe	Asn	Lys	Lys		
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Pro	Ile	Leu	Phe	Phe	Leu	Asn	Asp	Ala	Arg	Ala	Asp	Gln	Ser	Arg	Val		
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Gly	Leu	Met	His	Ile	Gly	Val	Phe	Ile	Leu	Leu	Leu	Leu	Ser	Gly	Glu		
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Met	Asp	Ile	Pro	Val	Phe	Thr	Gly	Thr	His	Ala	Asp	Leu	Leu	Ile	Val		
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Val	Phe	His	Lys	Ile	Ile	Thr	Ser	Gly	His	Gln	Arg	Leu	Gln	Pro	Leu		
465				470					475						480		
Phe	Asp	Cys	Leu	Leu	Thr	Ile	Val	Val	Asn	Val	Ser	Pro	Tyr	Leu	Lys		
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Ser	Leu	Ser	Met	Val	Thr	Ala	Asn	Lys	Leu	Leu	His	Leu	Leu	Glu	Ala		
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Phe	Ser	Thr	Thr	Trp	Phe	Leu	Phe	Ser	Ala	Ala	Gln	Asn	His	His	Leu		
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Phe	His	Gln	Leu	Ala	Asn	Leu	Pro	Thr	Asp	Pro	Pro	Thr	Ile	His	Lys		
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Glu	Pro	Gly	Thr	Leu	Lys	Thr	Ser	Leu	Val	Ala	Thr	Pro	Gly	Ile	Asp		
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Lys	Leu	Thr	Glu	Lys	Ser	Gln	Val	Ser	Glu	Asp	Gly	Thr	Leu	Arg	Ser		
625				630					635						640		
Leu	Glu	Pro	Glu	Pro	Gln	Gln	Ser	Leu	Glu	Asp	Gly	Ser	Pro	Ala	Lys		
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	660		665		670
Ser Ala	Ser Gly Gln Trp	Ser Pro Thr Pro Glu Trp	Val Leu Ser Trp		
	675	680	685		
Lys Ser	Lys Leu Pro Leu Gln Thr Ile Met Arg	Leu Leu Gln Val Leu			
	690	695	700		
Val Pro	Gln Val Glu Lys Ile Cys Ile Asp Lys Gly Leu Thr Asp Glu				
705		710	715		720
Ser Glu	Ile Leu Arg Phe Leu Gln His Gly Thr Leu Val Gly Leu Leu				
	725	730	735		
Pro Val	Pro His Pro Ile Leu Ile Arg Lys Tyr Gln Ala Asn Ser Gly				
	740	745	750		
Thr Ala	Met Trp Phe Arg Thr Tyr Met Trp Gly Val Ile Tyr Leu Arg				
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<210> 343
 <211> 563
 <212> DNA
 <213> Homo sapiens

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 <211> 107
 <212> PRT
 <213> Homo sapiens

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 Ile Gly Thr Leu Glu Arg His Thr Lys Lys Thr Gly Phe Glu Lys Thr
 35 40 45
 Ser Ala Ile Ala Asn Val Ala Lys Ile Gln Thr Leu Asp Ala Leu Asn
 50 55 60
 Asp Ala Leu Glu Lys Leu Asn Tyr Lys Phe Pro Ala Thr Val His Met
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 Ala His Gln Lys Pro Thr Pro Ala Leu Glu Lys Val Val Pro Leu Lys
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<210> 345
 <211> 3733
 <212> DNA
 <213> Homo sapiens

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356

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<210> 346

<211> 639

<212> PRT

<213> Homo sapiens

<400> 346

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 20          25          30
Leu His Pro Pro His His Thr Leu His Gln Thr Val Thr Ala Gln Ala
 35          40          45
Ser Lys His Ser Pro Glu Ala Arg Tyr Arg Leu Asp Phe Gly Glu Ser
 50          55          60
Gln Asp Trp Val Leu Glu Ala Glu Asp Glu Gly Glu Glu Tyr Ser Pro
 65          70          75          80
Leu Glu Gly Leu Pro Pro Phe Ile Ser Leu Arg Glu Asp Gln Leu Leu
 85          90          95
Val Ala Val Ala Leu Pro Gln Ala Arg Arg Asn Gln Ser Gln Gly Arg
100          105          110
Arg Gly Gly Ser Tyr Arg Leu Ile Lys Gln Pro Arg Arg Gln Asp Lys
115          120          125
Glu Ala Pro Lys Arg Asp Trp Gly Ala Asp Glu Asp Gly Glu Val Ser
130          135          140
Glu Glu Glu Glu Leu Thr Pro Phe Ser Leu Asp Pro Arg Gly Leu Gln
145          150          155          160
Glu Ala Leu Ser Ala Arg Ile Pro Leu Gln Arg Ala Leu Pro Glu Val
165          170          175
Arg His Pro Leu Cys Leu Gln Gln His Pro Gln Asp Ser Leu Pro Thr
180          185          190
Ala Ser Val Ile Leu Cys Phe His Asp Glu Ala Trp Ser Thr Leu Leu
195          200          205
Arg Thr Val His Ser Ile Leu Asp Thr Val Pro Arg Ala Phe Leu Lys
210          215          220
Glu Ile Ile Leu Val Asp Asp Leu Ser Gln Gln Gly Gln Leu Lys Ser
225          230          235          240
Ala Leu Ser Glu Tyr Val Ala Arg Leu Glu Gly Val Lys Leu Leu Arg
245          250          255
Ser Asn Lys Arg Leu Gly Ala Ile Arg Ala Arg Met Leu Gly Ala Thr
260          265          270
Arg Ala Thr Gly Asp Val Leu Val Phe Met Asp Ala His Cys Glu Cys

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275	280	285
His Pro Gly Trp Leu Glu	Pro Leu Leu Ser Arg	Ile Ala Gly Asp Arg
290	295	300
Ser Arg Val Val Ser Pro	Val Ile Asp Val Ile	Asp Trp Lys Thr Phe
305	310	315
Gln Tyr Tyr Pro Ser Lys	Asp Leu Gln Arg Gly	Val Leu Asp Trp Lys
325	330	335
Leu Asp Phe His Trp Glu	Pro Leu Pro Glu His	Val Arg Lys Ala Leu
340	345	350
Gln Ser Pro Ile Ser Pro	Ile Arg Ser Pro Val	Val Pro Gly Glu Val
355	360	365
Val Ala Met Asp Arg His	Tyr Phe Gln Asn Thr	Gly Ala Tyr Asp Ser
370	375	380
Leu Met Ser Leu Arg Gly	Gly Glu Asn Leu Glu	Leu Ser Phe Lys Ala
385	390	395
Trp Leu Cys Gly Gly Ser	Val Glu Ile Leu Pro	Cys Ser Arg Val Gly
405	410	415
His Ile Tyr Gln Asn Gln	Asp Ser His Ser Pro	Leu Asp Gln Glu Ala
420	425	430
Thr Leu Arg Asn Arg Val	Arg Ile Ala Glu Thr	Trp Leu Gly Ser Phe
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Lys Glu Thr Phe Tyr Lys	His Ser Pro Glu Ala	Phe Ser Leu Ser Lys
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485	490	495
Tyr Pro Ser Glu Pro Arg	Pro Ser Phe Ser Gly	Lys Leu His Asn Thr
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515	520	525
Cys Pro Met Val Leu Ala	Pro Cys Ser Asp Ser	Arg Gln Gln Gln Tyr
530	535	540
Leu Gln His Thr Ser Arg	Lys Glu Ile His Phe	Gly Ser Pro Gln His
545	550	555
Leu Cys Phe Ala Val Arg	Gln Glu Gln Val Ile	Leu Gln Asn Cys Thr
565	570	575
Glu Glu Gly Leu Ala Ile	His Gln Gln His Trp	Asp Phe Gln Glu Asn
580	585	590
Gly Met Ile Val His Ile	Leu Ser Gly Lys Cys	Met Glu Ala Val Val
595	600	605
Gln Glu Asn Asn Lys Asp	Leu Tyr Leu Arg Pro	Cys Asp Gly Lys Ala
610	615	620
Arg Gln Gln Trp Arg Phe	Asp Gln Ile Asn Ala	Val Asp Glu Arg
625	630	635

<210> 347
 <211> 1891
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(1891)
 <223> n = A,T,C or G

<400> 347

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tattctggct ggagcaattg cactcatcat tggctttggt atttcagggg gacactccat 180
cacagtcaact actgtcgctt cagctgggaa cattggggag gatggaatcc tgagctgcac 240
ttttgaacct gacatcaaac tttctgatat cgtgatacaa tggctgaagg aagggtgttt 300
aggcttggtc catgagttca aagaaggcaa agatgagctg tcggagcagg atgaaatgtt 360
cagaggccgg acagcagtggt ttgctgatca agtgatagtt ggcaatgcct ctttgcggt 420
gaaaaacgtg caactcacag atgctggcac ctacaaatgt tatatcatca cttctaaagg 480
caaggggaaat gctaaccctt agtataaaac tggagccttc agcatgccgg aagtgaatgt 540
ggactataat gccagctcag agaccttgcg gtgtgagggt ccccgatggt tccccagcc 600
cacagtggtc tgggcatccc aagttgacca gggagccaac ttctcggaag tctccaatac 660
cagctttgag ctgaactctg agaatgtgac catgaagggt gtgtctgtgc tctacaatgt 720
tacgatcaac aacacatact cctgtatgat tgaaaatgac attgccaaag caacagggga 780
tatcaaagtg acagaatcgg agatcaaaaag gcggagtcac ctacagctgc taaactcaaa 840
ggcttctctg tgtgtctctt ctttctttgc catcagctgg gcacttctgc ctctcagccc 900
ttacctgatg ctaaaataat gtgcctcggc cacaaaaaag catgcaaagt cattgttaca 960
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cctgcaagcc aagttctgta agagaaatgc ctgagttcta gctcagggtt tcttactctg 1500
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tccatgaang cacacacaga cttttgaaag caaggacaat gactgcttga attgaggcct 1620
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nactgntatt nacatngttg tttnatagaa aanncntgat tttaganngt tncctgnatc 1800
nttcaagna gaatgnattw aaaatatacy attttccbaa aaaaaaaaaa aaaaaaaaaa 1860
maaagtacct cggccgcgac cacgctaagg g 1891

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<210> 348

<211> 282

<212> PRT

<213> Homo sapiens

<400> 348

```

Met Ala Ser Leu Gly Gln Ile Leu Phe Trp Ser Ile Ile Ser Ile Ile
1           5           10          15
Ile Ile Leu Ala Gly Ala Ile Ala Leu Ile Ile Gly Phe Gly Ile Ser
20          25          30
Gly Arg His Ser Ile Thr Val Thr Val Ala Ser Ala Gly Asn Ile
35          40          45
Gly Glu Asp Gly Ile Leu Ser Cys Thr Phe Glu Pro Asp Ile Lys Leu
50          55          60
Ser Asp Ile Val Ile Gln Trp Leu Lys Glu Gly Val Leu Gly Leu Val
65          70          75          80
His Glu Phe Lys Glu Gly Lys Asp Glu Leu Ser Glu Gln Asp Glu Met
85          90          95
Phe Arg Gly Arg Thr Ala Val Phe Ala Asp Gln Val Ile Val Gly Asn
100         105         110
Ala Ser Leu Arg Leu Lys Asn Val Gln Leu Thr Asp Ala Gly Thr Tyr
115         120         125
Lys Cys Tyr Ile Ile Thr Ser Lys Gly Lys Gly Asn Ala Asn Leu Glu
130         135         140
Tyr Lys Thr Gly Ala Phe Ser Met Pro Glu Val Asn Val Asp Tyr Asn

```

359

145		150		155		160
Ala Ser Ser Glu Thr	Leu Arg Cys Glu Ala	Pro Arg Trp Phe	Pro Gln			
	165	170	175			
Pro Thr Val Val Trp	Ala Ser Gln Val Asp	Gln Gly Ala Asn	Phe Ser			
	180	185	190			
Glu Val Ser Asn Thr	Ser Phe Glu Leu Asn	Ser Glu Asn Val	Thr Met			
	195	200	205			
Lys Val Val Ser Val	Leu Tyr Asn Val Thr	Ile Asn Asn Thr	Tyr Ser			
	210	215	220			
Cys Met Ile Glu Asn	Asp Ile Ala Lys Ala	Thr Gly Asp Ile	Lys Val			
225	230	235	240			
Thr Glu Ser Glu Ile	Lys Arg Arg Ser His	Leu Gln Leu Leu	Asn Ser			
	245	250	255			
Lys Ala Ser Leu Cys	Val Ser Ser Phe Phe	Ala Ile Ser Trp	Ala Leu			
	260	265	270			
Leu Pro Leu Ser Pro	Tyr Leu Met Leu	Lys				
	275	280				

<210> 349
 <211> 1517
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc_feature
 <222> (1)...(1517)
 <223> n = A,T,C or G

<400> 349

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gccccttagc	ccccgcccc	agctgccagt	ccccagcagc	tcagtcctgc	agtgagagtc	180
ttgggagtc	atagctaagc	accaggagct	gagcactgcc	cgctgtgcct	gcctgcaagt	240
ctgacatggc	tcaggagaaa	atggagctgg	accttgagcc	tgacacatct	tatgggggaa	300
ccctgaggag	atccagcagc	gctcccctaa	tccatgggct	cagtgcacctt	tcacagggtt	360
tccaacctta	cacacttaga	actcggagga	atagtacaac	aattatgagc	cgtcacagcc	420
tggagaagg	cctggatatg	gtgaacagag	aaactgcaca	tgaaagggaa	atgcaaacgg	480
caatgcagat	aagccaatca	tgggatgaga	gcttgagcct	gagtgcagct	gattttgaca	540
agccggagaa	attatattct	cctaagagaa	ttgacttcac	tccagtttct	ccagcacctt	600
cacccaccag	gggattcgga	aagatgttcg	tgagcagcag	tggattgcca	ccaagtccag	660
ttcccagtc	aagacgattt	tcaagcagga	gaagtcagag	tccagtcaag	tgcattagac	720
ccagtgttct	tggtcctctt	aaaagaaaag	gtgaaatgga	gacagaaaag	cagcccaaga	780
gactcttcca	aggcactacc	aatatgttat	ctccagatgc	cgcgcaactg	tctgatctca	840
gttcatgttc	agatattttg	gatggcagta	gtagcagcag	tggcttatcc	tcagacccgc	900
tggctaaagg	cagcgctacc	gcagagtctc	cagtagcatg	ctccaattca	tgctcttcgt	960
tcattctgat	ggatgatctc	tcacccaagt	gacttaacca	tttctgattc	aacgttttaa	1020
ctgctgtttc	ctacataaaa	tgtttagtgg	ggaacgcaga	gaactttgat	ccataatgag	1080
gattaaagtt	ttacagattt	cacacattct	gatgctatta	ttactctttg	gcattctctt	1140
tctccaaagt	tcaattttgt	gagcctagt	accttactag	tatctggttt	tgctgatctc	1200
attttgatt	tagtgattaa	atctcaaatg	ctgatttttg	attgcttaga	ggaatctttt	1260
ttcttagtgc	ctcaaaaaac	acctattttg	agtctataca	tttaagaaag	gcactgatgt	1320
gtattgcctt	taatgggtcc	ttttccgcag	caagtgatat	gacagatttg	atcagaaatt	1380
ctcttgcttg	agagattttt	ttttgtcctc	tgttgactac	atagtttcaa	atctctcttt	1440
atttcatgat	gatataataa	ttgcttttaa	ttatatnaaa	ttttattttc	tggtatcagct	1500
tcaagaccat	tatttttg					1517

<210> 350

360

<211> 243
 <212> PRT
 <213> Homo sapiens

<220>
 <221> VARIANT
 <222> (1)...(243)
 <223> Xaa = Any Amino Acid

<400> 350

Met	Ala	Gln	Glu	Lys	Met	Glu	Leu	Asp	Leu	Glu	Pro	Asp	Thr	Ser	Tyr
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Gly	Gly	Thr	Leu	Arg	Arg	Ser	Ser	Ser	Ala	Pro	Leu	Ile	His	Gly	Leu
			20					25					30		
Ser	Asp	Leu	Ser	Gln	Val	Phe	Gln	Pro	Tyr	Thr	Leu	Arg	Thr	Arg	Arg
		35					40					45			
Asn	Ser	Thr	Thr	Ile	Met	Ser	Arg	His	Ser	Leu	Glu	Glu	Gly	Leu	Asp
		50					55					60			
Met	Val	Asn	Arg	Glu	Thr	Ala	His	Glu	Arg	Glu	Met	Gln	Thr	Ala	Met
					70					75					80
Gln	Ile	Ser	Gln	Ser	Trp	Asp	Glu	Ser	Leu	Ser	Leu	Ser	Asp	Ser	Asp
				85					90					95	
Phe	Asp	Lys	Pro	Glu	Lys	Leu	Tyr	Ser	Pro	Lys	Arg	Ile	Asp	Phe	Thr
			100						105					110	
Pro	Val	Ser	Pro	Ala	Pro	Ser	Pro	Thr	Arg	Gly	Phe	Gly	Lys	Met	Phe
			115					120					125		
Val	Ser	Ser	Ser	Gly	Leu	Pro	Pro	Ser	Pro	Val	Pro	Ser	Pro	Arg	Arg
						135					140				
Phe	Ser	Ser	Arg	Arg	Ser	Gln	Ser	Pro	Val	Lys	Cys	Ile	Arg	Pro	Ser
						150				155					160
Val	Leu	Gly	Pro	Leu	Lys	Arg	Lys	Gly	Glu	Met	Glu	Thr	Glu	Ser	Gln
					165					170					175
Pro	Lys	Arg	Leu	Phe	Gln	Gly	Thr	Thr	Asn	Met	Leu	Ser	Pro	Asp	Ala
					180				185					190	
Ala	Gln	Leu	Ser	Asp	Leu	Ser	Ser	Cys	Ser	Asp	Ile	Leu	Asp	Gly	Ser
							200					205			
Ser	Ser	Ser	Ser	Gly	Leu	Ser	Ser	Asp	Pro	Leu	Ala	Xaa	Xaa	Gln	Arg
							215					220			
Tyr	Arg	Arg	Val	Ser	Ser	Ser	Met	Leu	Gln	Phe	Met	Leu	Phe	Val	His
						230				235					240
Leu	Asp	Gly													

<210> 351
 <211> 248
 <212> PRT
 <213> Homo sapiens

<400> 351

Met	Ala	Gln	Glu	Lys	Met	Glu	Leu	Asp	Leu	Glu	Pro	Asp	Thr	Ser	Tyr
1				5					10					15	
Gly	Gly	Thr	Leu	Arg	Arg	Ser	Ser	Ser	Ala	Pro	Leu	Ile	His	Gly	Leu
			20					25					30		
Ser	Asp	Leu	Ser	Gln	Val	Phe	Gln	Pro	Tyr	Thr	Leu	Arg	Thr	Arg	Arg
			35				40					45			
Asn	Ser	Thr	Thr	Ile	Met	Ser	Arg	His	Ser	Leu	Glu	Glu	Gly	Leu	Asp
							55					60			

361

Met Val Asn Arg Glu Thr Ala His Glu Arg Glu Met Gln Thr Ala Met
65 70 75 80
Gln Ile Ser Gln Ser Trp Asp Glu Ser Leu Ser Leu Ser Asp Ser Asp
85 90 95
Phe Asp Lys Pro Glu Lys Leu Tyr Ser Pro Lys Arg Ile Asp Phe Thr
100 105 110
Pro Val Ser Pro Ala Pro Ser Pro Thr Arg Gly Phe Gly Lys Met Phe
115 120 125
Val Ser Ser Ser Gly Leu Pro' Pro Ser Pro Val Pro Ser Pro Arg Arg
130 135 140
Phe Ser Ser Arg Arg Ser Gln Ser Pro Val Lys Cys Ile Arg Pro Ser
145 150 155 160
Val Leu Gly Pro Leu Lys Arg Lys Gly Glu Met Glu Thr Glu Ser Gln
165 170 175
Pro Lys Arg Leu Phe Gln Gly Thr Thr Asn Met Leu Ser Pro Asp Ala
180 185 190
Ala Gln Leu Ser Asp Leu Ser Ser Cys Ser Asp Ile Leu Asp Gly Ser
195 200 205
Ser Ser Ser Ser Gly Leu Ser Ser Asp Pro Leu Ala Lys Gly Ser Ala
210 215 220
Thr Ala Glu Ser Pro Val Ala Cys Ser Asn Ser Cys Ser Ser Phe Ile
225 230 235 240
Leu Met Asp Asp Leu Ser Pro Lys
245

<210> 352

<211> 1529

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(1529)

<223> n = A,T,C or G

<400> 352

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gccccttagc ccccgcccc agctgccagt cccagcagc tcagtcctgc agtgagagtc 180
ttgggagtc atagctaagc accaggagct gagcactgcc cgctgtgcct gcctgcaagt 240
ctgacatggc tcaggagaaa atggagctgg accttgagcc tgacacatct tatgggggaa 300
ccctgaggag atccagcagc gctcccctaa tccatgggct cagtgcctt tcacaggttt 360
tccaacctta cacacttaga actcggagga atagtacaac aattatgagc cgtcacagcc 420
tggttaagtat agaagaagaa ggccctggata tggatgaacag agaaactgca catgaaagg 480
aaatgcaaac ggcaatgcag ataagccaat catgggatga gagcttgagc ctgagtgaca 540
gtgatattga caagccggag aaattatatt ctccctaagag aattgacttc actccagttt 600
ctccagcacc ttcacccacc aggggattcg gaaagatgtt cgtgagcagc agtggattgc 660
caccaagtcc agttcccagt ccaagacgat tttcaagcag gagaagtcag agtccagtca 720
agtgcattag acccagtgtt cttggtcctc ttaaaagaaa aggtgaaatg gagacagaaa 780
gtcagcccaa gagactcttc caaggcacta ccaatatgtt atctccagat gccgcgcaac 840
tgtctgatct cagttcatgt tcagatattt tggatggcag tagtagcagc agtggcttat 900
cctcagaccc gctggctaaa ggcagcgcta ccgcagagtc tccagtagca tgctccaatt 960
catgctcttc gttcatcttg atggatgatc tctcacccaa gtgacttaac catttctgat 1020
tcaacgtttt aactgctgtt tcctacataa aatgttttagt ggggaacgca gagaactttg 1080
atccataatg aggattaaag ttttacagat ttcacacatt ctgatgctat tattactctt 1140
tggcatctct cttctccaaa gttcaatttt gtgagcctag tgaccttact agtatctggt 1200
tttgctgatc tcatttttga ttttagtgatt aaatctcaaa tgctgatttt tgattgctta 1260

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362

```

gaggaatctt ttttcttagt gcctcaaaaa acacctatct tgagtctata catttaagaa 1320
aggcactgat gtgtattgcc tttaatgggt ccttttccgc agcaagtgat atgacagatt 1380
tgatcagaaa ttctcttgct tgagagattt ttttttgtcc tctgttgact acatagtttc 1440
aaatctctct ttatttcatt atgatataata aattgctttt aattatatna aattttattt 1500
tctggatcag cttcaagacc attatttttg 1529

```

<210> 353

<211> 252

<212> PRT

<213> Homo sapiens

<400> 353

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Met Ala Gln Glu Lys Met Glu Leu Asp Leu Glu Pro Asp Thr Ser Tyr
 1           5           10           15
Gly Gly Thr Leu Arg Arg Ser Ser Ser Ala Pro Leu Ile His Gly Leu
 20           25           30
Ser Asp Leu Ser Gln Val Phe Gln Pro Tyr Thr Leu Arg Thr Arg Arg
 35           40           45
Asn Ser Thr Thr Ile Met Ser Arg His Ser Leu Val Ser Ile Glu Glu
 50           55           60
Glu Gly Leu Asp Met Val Asn Arg Glu Thr Ala His Glu Arg Glu Met
 65           70           75           80
Gln Thr Ala Met Gln Ile Ser Gln Ser Trp Asp Glu Ser Leu Ser Leu
 85           90           95
Ser Asp Ser Asp Phe Asp Lys Pro Glu Lys Leu Tyr Ser Pro Lys Arg
100          105          110
Ile Asp Phe Thr Pro Val Ser Pro Ala Pro Ser Pro Thr Arg Gly Phe
115          120          125
Gly Lys Met Phe Val Ser Ser Ser Gly Leu Pro Pro Ser Pro Val Pro
130          135          140
Ser Pro Arg Arg Phe Ser Ser Arg Arg Ser Gln Ser Pro Val Lys Cys
145          150          155          160
Ile Arg Pro Ser Val Leu Gly Pro Leu Lys Arg Lys Gly Glu Met Glu
165          170          175
Thr Glu Ser Gln Pro Lys Arg Leu Phe Gln Gly Thr Thr Asn Met Leu
180          185          190
Ser Pro Asp Ala Ala Gln Leu Ser Asp Leu Ser Ser Cys Ser Asp Ile
195          200          205
Leu Asp Gly Ser Ser Ser Ser Ser Gly Leu Ser Ser Asp Pro Leu Ala
210          215          220
Lys Gly Ser Ala Thr Ala Glu Ser Pro Val Ala Cys Ser Asn Ser Cys
225          230          235          240
Ser Ser Phe Ile Leu Met Asp Asp Leu Ser Pro Lys
245          250

```

<210> 354

<211> 1574

<212> DNA

<213> Homo sapiens

<220>

<221> misc_feature

<222> (1)...(1574)

<223> n = A,T,C or G

<400> 354

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```

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gccccttagc ccccgccccc agctgccagt ccccgagcgc tcagtcctgc agtgagagtc 180
ttgggagtc atagctaagc accaggagct gagcactgcc cgctgtgcct gcctgcaagt 240
ctgacatggc tcaggagaaa atggagctgg accttgagcc tgacacatct tatgggggaa 300
ccctgaggag atccagcagc gctcccctaa tccatgggct cagtgcctt tcacagggtt 360
tccaacctta cacacttaga actcggagga atagtacaac aattatgagc cgtcacagcc 420
tgttgctgtc atctcacct aatcgtattc ctgtagcag actgcatcag atcaaaaggg 480
aagaaggcct ggatatggtg aacagagaaa ctgcacatga aagggaatg caaacggcaa 540
tgcagataag ccaatcatgg gatgagagct tggcctgag tgacagtgt tttgacaagc 600
cggagaaatt atattctcct aagagaattg acttcactcc agtttctcca gcaccttcac 660
ccaccagggg attcggaaag atgttcgtga gcagcagtgg attgccacca agtccagttc 720
ccagtccaag acgattttca agcaggagaa gtcagagtc agtcaagtgc attagacca 780
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taaagtttta cagatttcac acattctgat gctattatta ctctttggca tctctcttct 1200
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tcatgatgat atataaattg cttttaatta tatnaaattt tattttctgg atcagcttca 1560
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```

<210> 355

<211> 267

<212> PRT

<213> Homo sapiens

<400> 355

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Met Ala Gln Glu Lys Met Glu Leu Asp Leu Glu Pro Asp Thr Ser Tyr
1          5          10          15
Gly Gly Thr Leu Arg Arg Ser Ser Ser Ala Pro Leu Ile His Gly Leu
20          25          30
Ser Asp Leu Ser Gln Val Phe Gln Pro Tyr Thr Leu Arg Thr Arg Arg
35          40          45
Asn Ser Thr Thr Ile Met Ser Arg His Ser Leu Leu Leu Ser Ser Ser
50          55          60
Pro Asn Arg Ile Pro Ser Arg Leu His Gln Ile Lys Arg Glu Glu
65          70          75          80
Gly Leu Asp Met Val Asn Arg Glu Thr Ala His Glu Arg Glu Met Gln
85          90          95
Thr Ala Met Gln Ile Ser Gln Ser Trp Asp Glu Ser Leu Ser Leu Ser
100          105          110
Asp Ser Asp Phe Asp Lys Pro Glu Lys Leu Tyr Ser Pro Lys Arg Ile
115          120          125
Asp Phe Thr Pro Val Ser Pro Ala Pro Ser Pro Thr Arg Gly Phe Gly
130          135          140
Lys Met Phe Val Ser Ser Ser Gly Leu Pro Pro Ser Pro Val Pro Ser
145          150          155          160
Pro Arg Arg Phe Ser Ser Arg Arg Ser Gln Ser Pro Val Lys Cys Ile
165          170          175
Arg Pro Ser Val Leu Gly Pro Leu Lys Arg Lys Gly Glu Met Glu Thr
180          185          190
Glu Ser Gln Pro Lys Arg Leu Phe Gln Gly Thr Thr Asn Met Leu Ser

```

364

195	200	205
Pro Asp Ala Ala Gln Leu Ser Asp Leu Ser Ser Cys Ser Asp Ile Leu		
210	215	220
Asp Gly Ser Ser Ser Ser Ser Gly Leu Ser Ser Asp Pro Leu Ala Lys		
225	230	235
Gly Ser Ala Thr Ala Glu Ser Pro Val Ala Cys Ser Asn Ser Cys Ser		
245	250	255
Ser Phe Ile Leu Met Asp Asp Leu Ser Pro Lys		
260	265	

<210> 356
 <211> 4458
 <212> DNA
 <213> Homo sapiens

<400> 356

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cagaccaacc ggctggcagc ccagctccgc tccgcccgc cctgcctcgg accctgcgcc 180
tgaggaagta tcgaggcaac cctctgccac ccgaagtctg tgggtcgctc ccagagggcg 240
cgccctggag ccgagcgccc ttgggcggcc atctggaggc caggtgcggg ccgcgaaccc 300
gcgaggagcg cgcggcgggc gcggcggcga cggcaggagg aggggcggg agcccgggcg 360
ccgccgaagg acgccccgtc ctccacatgc tgccacttgg ctgagccggg cgccggcgag 420
aaggcggcgc cgtgcccctg gcagctggac tgcactttgc ccccgcccg cctcagctgc 480
cgcccgccca gacgccagca agccccctc ccacgacagg gctgctccgg gagcttcgga 540
gacccgcccc gggcctgagc gcaggtgcc tccgggaccc caggtctgtc cggacgtgcc 600
atgggcgcgc agctgcggg caacgtgttg tgtaagtga catctgggag gtaaacacta 660
cacgtgaaga gtggtgaaag ggaacattga ttactgaagt gccctggaga gggaaagcac 720
tggtcaacat cacatggaca aatttcattg ttttctaaag atggcctgga agtagtcttt 780
gccactgctt cctccacaaa cagctcttca taacatgggc tgcatgaaat caaagcaaac 840
tttcccattt cctaccatat atgaaggatga gaagcagcat gagagtgaag aaccctttat 900
gccagaagag agatgtctac ctaggatggc ttctccagtt aatgtcaaag aggaagtga 960
ggaacctcca gggaccaata ttgtgatctt ggaatatgca caccgcctgt ctcaggatat 1020
cttgtgtgat gccttgcagc aatgggcatg caataacatc aagtaccatg acattccata 1080
cattgagagt gaggggcctt gaggtgttag gatgacaaca ctttgactgt ggaggtgcta 1140
gtttgaataa atgtgacaaa agcaaaaact ggtgtgaaaa agtacaataa actatctgga 1200
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<210> 357

<211> 127

<212> PRT

<213> Homo sapiens

<400> 357

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<211> 583

<212> DNA

<213> Homo sapiens

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 <212> PRT
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 35             40             45
Cys Val Ser Asp Ser Glu Cys Ala Asp Asn Leu Lys Cys Cys Ser Ala
 50             55             60
Gly Cys Ala Thr Phe Cys Leu Leu Cys Pro Asn Asp Lys Glu Gly Ser
 65             70             75             80
Cys Pro Gln Val Asn Ile Asn Phe Pro Gln Leu Gly Leu Cys Arg Asp
 85             90             95
Gln Cys Gln Val Asp Thr Gln Cys Pro Gly Gln Met Lys Cys Cys Arg
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 115             120             125

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 <211> 3310
 <212> DNA
 <213> Homo sapiens

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369

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<210> 363

<211> 732

<212> PRT

<213> Homo sapiens

<400> 363

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Gln Ala Lys Lys Val Ile Thr Met Phe Val Gln Arg Gln Val Phe Ala
35          40          45
Glu Asn Lys Asp Glu Ile Ala Leu Val Leu Phe Gly Thr Asp Gly Thr
50          55          60
Asp Asn Pro Leu Ser Gly Gly Asp Gln Tyr Gln Asn Ile Thr Val His
65          70          75          80
Arg His Leu Met Leu Pro Asp Phe Asp Leu Leu Glu Asp Ile Glu Ser
85          90          95

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Lys Ile Gln Pro Gly Ser Gln Gln Ala Asp Phe Leu Asp Ala Leu Ile
 100 105 110
 Val Ser Met Asp Val Ile Gln His Glu Thr Ile Gly Lys Lys Phe Glu
 115 120 125
 Lys Arg His Ile Glu Ile Phe Thr Asp Leu Ser Ser Arg Phe Ser Lys
 130 135 140
 Ser Gln Leu Asp Ile Ile His Ser Leu Lys Lys Cys Asp Ile Ser
 145 150 155 160
 Leu Gln Phe Phe Leu Pro Phe Ser Leu Gly Lys Glu Asp Gly Ser Gly
 165 170 175
 Asp Arg Gly Asp Gly Pro Phe Arg Leu Gly Gly His Gly Pro Ser Phe
 180 185 190
 Pro Leu Lys Gly Ile Thr Glu Gln Gln Lys Glu Gly Leu Glu Ile Val
 195 200 205
 Lys Met Val Met Ile Ser Leu Glu Gly Glu Asp Gly Leu Asp Glu Ile
 210 215 220
 Tyr Ser Phe Ser Glu Ser Leu Arg Lys Leu Cys Val Phe Lys Lys Ile
 225 230 235 240
 Glu Arg His Ser Ile His Trp Pro Cys Arg Leu Thr Ile Gly Ser Asn
 245 250 255
 Leu Ser Ile Arg Ile Ala Ala Tyr Lys Ser Ile Leu Gln Glu Arg Val
 260 265 270
 Lys Lys Thr Trp Thr Val Val Asp Ala Lys Thr Leu Lys Lys Glu Asp
 275 280 285
 Ile Gln Lys Glu Thr Val Tyr Cys Leu Asn Asp Asp Asp Glu Thr Glu
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 Val Leu Lys Glu Asp Ile Ile Gln Gly Phe Arg Tyr Gly Ser Asp Ile
 305 310 315 320
 Val Pro Phe Ser Lys Val Asp Glu Glu Gln Met Lys Tyr Lys Ser Glu
 325 330 335
 Gly Lys Cys Phe Ser Val Leu Gly Phe Cys Lys Ser Ser Gln Val Gln
 340 345 350
 Arg Arg Phe Phe Met Gly Asn Gln Val Leu Lys Val Phe Ala Ala Arg
 355 360 365
 Asp Asp Glu Ala Ala Val Ala Leu Ser Ser Leu Ile His Ala Leu
 370 375 380
 Asp Asp Leu Asp Met Val Ala Ile Val Arg Tyr Ala Tyr Asp Lys Arg
 385 390 395 400
 Ala Asn Pro Gln Val Gly Val Ala Phe Pro His Ile Lys His Asn Tyr
 405 410 415
 Glu Cys Leu Val Tyr Val Gln Leu Pro Phe Met Glu Asp Leu Arg Gln
 420 425 430
 Tyr Met Phe Ser Ser Leu Lys Asn Ser Lys Lys Tyr Ala Pro Thr Glu
 435 440 445
 Ala Gln Leu Asn Ala Val Asp Ala Leu Ile Asp Ser Met Ser Leu Ala
 450 455 460
 Lys Lys Asp Glu Lys Thr Asp Thr Leu Glu Asp Leu Phe Pro Thr Thr
 465 470 475 480
 Lys Ile Pro Asn Pro Arg Phe Gln Arg Leu Phe Gln Cys Leu Leu His
 485 490 495
 Arg Ala Leu His Pro Arg Glu Pro Leu Pro Pro Ile Gln Gln His Ile
 500 505 510
 Trp Asn Met Leu Asn Pro Pro Ala Glu Val Thr Thr Lys Ser Gln Ile
 515 520 525
 Pro Leu Ser Lys Ile Lys Thr Leu Phe Pro Leu Ile Glu Ala Lys Lys
 530 535 540
 Lys Asp Gln Val Thr Ala Gln Glu Ile Phe Gln Asp Asn His Glu Asp
 545 550 555 560

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Gly	Pro	Thr	Ala	Lys	Lys	Leu	Lys	Thr	Glu	Gln	Gly	Gly	Ala	His	Phe
				565					570					575	
Ser	Val	Ser	Ser	Leu	Ala	Glu	Gly	Ser	Val	Thr	Ser	Val	Gly	Ser	Val
			580					585					590		
Asn	Pro	Ala	Glu	Asn	Phe	Arg	Val	Leu	Val	Lys	Gln	Lys	Lys	Ala	Ser
		595					600					605			
Phe	Glu	Glu	Ala	Ser	Asn	Gln	Leu	Ile	Asn	His	Ile	Glu	Gln	Phe	Leu
	610					615					620				
Asp	Thr	Asn	Glu	Thr	Pro	Tyr	Phe	Met	Lys	Ser	Ile	Asp	Cys	Ile	Arg
625					630					635					640
Ala	Phe	Arg	Glu	Glu	Ala	Ile	Lys	Phe	Ser	Glu	Glu	Gln	Arg	Phe	Asn
			645						650					655	
Asn	Phe	Leu	Lys	Ala	Leu	Gln	Glu	Lys	Val	Glu	Ile	Lys	Gln	Leu	Asn
			660					665					670		
His	Phe	Trp	Glu	Ile	Val	Val	Gln	Asp	Gly	Ile	Thr	Leu	Ile	Thr	Lys
		675					680					685			
Glu	Glu	Ala	Ser	Gly	Ser	Ser	Val	Thr	Ala	Glu	Glu	Ala	Lys	Lys	Phe
	690					695					700				
Leu	Ala	Pro	Lys	Asp	Lys	Pro	Ser	Gly	Asp	Thr	Ala	Ala	Val	Phe	Glu
705					710					715					720
Glu	Gly	Gly	Asp	Val	Asp	Asp	Leu	Leu	Asp	Met	Ile				
				725					730						